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Reports of the Special Investigation Committee on Surgical Shock and Allied Conditions

TRAUMATIC TOXAEMIA AS A FACTOR IN SHOCK

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REPORTS

OF THE

SPECIAL INVESTIGATION COMMITTEE ON SURGICAL SHOCK AND ALLIED CONDITIONS

VIII.—TRAUMATIC TOXAEMIA AS A FACTOR IN SHOCK

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TRAUMATIC TOXAEMIA AS A FACTOR IN SHOCK

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I. INTRODUCTORY

By Cuthbert S. Wallace, C.B., C.M.G.

When the war commenced it was generally held, as a result of animal experiments, that the state of shock was due to deficiency of blood or of the fluid contents of blood actually circulating.

Although, before the war, haemorrhage was accounted a contributory cause of shock by the clinician, it was doubtful if its effect in this direction was estimated at its true value. As the war went on clinical evidence accumulated to corroborate the experimental findings, for many surgeons found that they were unable accurately to distinguish the effects of haemorrhage from those of shock.

The task of the Military Surgeon differed in some particulars from that of the Civil Surgeon. The latter has been more concerned with the avoidance of shock, the former with shock already

established. It was recognized that besides haemorrhage, the presence of pain, cold, mental distress and rough handling were also contributory factors. At first, all these causes were taken as unavoidable under Service conditions, but the bad effects of rough usage as caused by transport were probably a surprise to many.

All the established methods of treatment were used, but warmth combined with rest greatly outstripped all others in favour. Stimulants dropped out of use, and vasoconstrictor drugs soon followed. Thus clinicians again found themselves in accord with the experimentalist.

As regards morphia, the British experience was that while moderate amounts were extremely useful, bad effects followed excessive doses.

The administration of fluids by the mouth and rectum were found very beneficial, but when the condition of the patient was more grave and normal saline was administered under the skin or into the veins, the result was very disappointing. Thus a fairly well established practice of civil surgery fell into disrepute.

The surgeon experienced another disappointment. If his measures were sufficient to put the soldier into a state that justified operation, this procedure produced a relapse. In many cases even if the general condition was sufficiently good at the end of the operation to give a hope of recovery, yet a fatal result followed. The added trauma of an operation necessary to save life again turned the balance against the patient.

In 1915 a definite improvement was brought about by the more rapid evacuation of the grievously wounded, thus showing that the time factor was important. A large series of abdominal operations showed that the low blood-pressure could not be attributed to a stagnation of blood in the visceral veins.

Until the spring of 1917 things remained in much the same condition, and the effort of the surgeon was directed towards curing shock.

At this date an investigation into the natural history of shock brought to notice the following facts.

(i) That the soldier was, even in trench warfare, on a limited supply of water, and consequently that there was no reservoir on which the circulation could draw in case of need. His condition in this respect much resembled that of the patient after the old-fashioned 'preparation for operation'.

(ii) That a patient possessed considerable recuperative powers in the early stages, for in transit to a C.C.S. a deterioration in general condition and a fall in blood-pressure could be remedied more than once by the simple process of rest, warmth, and the administration of fluids. The paramount importance of cutting down the time during which a state of shock was present was constantly impressed upon the surgeon as the war went on.

(iii) That shock could be divided into two varieties: (*a*) Primary, and (*b*) Secondary. Primary Shock, probable nervous in origin, might be absent, or if present could subside and be followed after a definite interval by Secondary Shock. It was Secondary Shock

that constituted the greater danger to the soldier, but at the same time—within limits—was under control of the surgeon. The nature of Primary Shock is undetermined, but it may be analogous to a faint or collapse. It may come on immediately on receipt of an injury, but in some instances only when the patient actually sees his own injury. It may be that it is the same condition as that which overtakes a person on the sudden receipt of bad news, or on realizing that he has had a narrow escape, or when the gravity of his condition becomes obvious to him. Something of a rather similar nature is seen in a perforated gastric ulcer in civil life; here the moment of perforating is marked by the onset of a grave condition that necessitates resuscitation measures before an operation can be undertaken.

The result of these findings was that measures till now largely confined to the C.C.S., were pushed forward up to the front line, and the patient was warmed, rested, supplied with fluid in various ways, and much more efficiently splinted. The development of shock was prevented, if possible, or, if it did develop, measures were at once taken to limit the time during which it was untreated. The good results were at once evident.

The recognition of the late onset of Secondary Wound Shock was of great importance. It did not refute the theory that shock might be the result of afferent impulses exhausting the vasomotor centre, but it opened the way for the conception of another cause of shock, namely the toxic; for under this theory time was required for the elaboration of the toxin.

Thus while it was possible to suppose that the continued irritation of a badly splinted fracture of the thigh could wear out the nervous centres, it was also possible to conceive that continued damage to the muscle by the bone fragments favoured the absorption of toxic products.

Experiments performed at a later period have proved that muscle injury can produce a state of shock, but it may be asked if clinical experience offers any evidence (*a*) that a toxaemia can produce such a condition of things; (*b*) whether muscle injury can provide a toxin. The available evidence is the following:

(i) The experience that, putting aside gross injuries, the shock from which the abdominally wounded man suffers, depends more on the loss of blood, or on peritonitis and sepsis, than on the extent of the lesion. Many men thought by the surgeon to have died of shock, have been proved by post-mortem examination to have died of acute sepsis or gas gangrene.

(ii) The improvement that follows the removal of a mangled limb.

(iii) The striking change for the better that follows excision of muscle infected by anaerobic bacilli.

(iv) The well-known association between shock and small multiple, or single large muscle wounds.

(v) The shocking nature of operations involving large muscle masses (amputation at hip).

About the same time that Secondary Wound Shock became

recognized attention was turned to three other points (*a*) the power of 'acidosis' to produce shock, (*b*) the discrepancy between the cutaneous capillary and venous count, (*c*) the bad effect of ordinary anaethesia. As regards (*a*) it has been proved that 'acidosis' can be neglected as a cause of shock, but (*b*) has an important bearing on the subject.

(*b*) It has been stated that operations on the abdomen clearly showed that the visceral vessels were not dilated, and that the theory of their dilatation accounting for the 'lost blood' could not be sustained. When the discrepancy between the cutaneous capillary and venous count became known it was thought that the concentration in the cutaneous capillaries might point to the lost fluid being located in the cutaneous tissues.

In this connexion it may be noted, that though the observations are few in number, blood counts taken from the mucous membrane of the mouth and from the intestinal vessels have shown no concentration.

The state of shock produced by histamine has been attributed partly to loss of fluid from the blood and partly to a general dilatation of the capillaries. An actual dilatation of the capillaries of the bowel is described as being present.

The vaso-constrictor theory of shock also looks to a passing of the blood fluids into the muscles and tissues.

In connexion with all these suggestions it can only be said that naked eye observations in man have not so far revealed oedema of the tissues or, with the possible exception of the skin, of dilated capillaries. Oedema, when it does occur, as in anaphylactic shock, is a very obvious phenomenon.

In certain cases, often referred to as 'blue men', there seems to be undoubtedly capillary dilatation or stasis, but these cases are the exception and not the rule.

On the other hand, it is hard to be sure of the state of the cutaneous capillaries from the colour of the skin, so that possibly, in the more common cases, when the skin is white or dusky, there may still be stasis and dilatation in this region.

(*c*) It has been previously stated that the act of operation was often sufficient to bring on again a state of shock. It now seems probable that a great deal of the bad effects were to be attributed to the anaesthetic. Chloroform had long been recognized as dangerous, but it was more evident that ether and other anaesthetics were far from harmless. Gas and oxygen was the least noxious, and with its wider adoption post-operative shock greatly diminished. Recent work seems to point to a toxic action of ether on the endothelial lining of the vessels, thus rendering it permeable to the blood fluids.

By this time hypertonic salines had been found useless and the gum solutions were coming into use. At first they were used in various strengths and for a time combined with bicarbonate of soda when acidosis was still considered a possible factor in shock. In the end the 6 per cent. solution of gum in normal saline became standard. This solution now entered into competition with trans-

fusion, which had risen to a prominent place in the treatment of shock. The comparative merits of blood and gum have been widely debated, and it cannot be said that the spheres of each have been defined, but it may be stated with confidence that in certain cases the gum solution has been of the utmost value.

Just before the war ended it was proved by the use of the vital red method that the shocked man as seen in the war had a reduced blood volume, which proof had been lacking up to date. It was also shown that a man's power of recovery was largely connected with the power of the circulation to take up fluid from the tissues, on the one hand, or to retain added fluid on the other. A certain class of case still possessed the power of dilution if the necessary fluid was in the tissues, or if it could be put there by administering fluid by one of the usual methods. In another class of case, while this power of dilution was feeble or wanting, yet the individual could retain fluid in his vessels provided a suitable fluid (blood or gum-saline) were introduced into his veins. In a third, both the above powers were lost, and treatment availed nothing.

While pain, cold, haemorrhage, continued trauma and toxaemia in various forms, and the time during which they are acting, are potent factors in producing shock as seen in war, it is not possible to exclude the nervous theory. There was a class of case in which none of the above factors were present to such a degree as to account for the state of shock. Sometimes the wounds were comparatively trivial and would not in ordinary course have been deemed capable of producing shock; sometimes the visible injuries were negligible. Two cases seen in the last days of the war may be mentioned. One was buried by the explosion of a shell in a cellar, the other was blown up by a buried shell over which he had lighted a fire. Both exhibited all the classic symptoms of shock, which lasted over forty-eight hours; in both treatment was of no avail. In neither did the post-mortem examination show any gross leison.

Some points of practical importance for the future seem to stand out.

(*a*) Shock is usually the result of several factors such as haemorrhage, toxins, cold, and anaesthetics.

The effect produced depends on the intensity of each, on the number that are acting at any one time, and on the duration of the period during which they are operative. Any one of these factors, encountered in a moderate degree and for a limited period, can be dealt with by the body. Thus, loss of blood is compensated for by an extraction of the fluid from the tissues; toxic products, provided they are thrown into the body in small amounts, are got rid of. If two occur together, then the effect produced is more than the sum of the two acting separately, and the body has difficulty in righting itself. If to these two factors be added a third, recovery may still be possible. On the other hand a fatal result may ensue if the body is further taxed by the administration of an anaesthetic, which to a normal individual would be comparatively harmless.

(*b*) It is important that the patient about to be submitted to an

operation should have a reserve of fluid on which he can draw. If fluid is lost it should be replaced without delay.

(*c*) The anaesthetic ether, hitherto thought comparatively harmless, may under certain conditions be of great danger to the patient.

II. THE ACTION OF HISTAMINE: ITS BEARING ON TRAUMATIC TOXAEMIA AS A FACTOR IN SHOCK

By H. H. Dale, P. P. Laidlaw, and A. N. Richards.

1. Introductory.

The shock with which we are concerned is that which during the war has been recognized as 'Secondary Shock'. For 'Primary Shock', the condition which Crile and his followers have distinguished as 'Collapse', a sufficient explanation seems to have been found as long ago as 1870, when Goltz demonstrated that a blow on the exposed mesentery of a suspended frog caused reflex inhibition of the heart through the vagus, and reflex dilatation of the arteries in the splanchnic area, in which the blood tended to collect by gravitation. Two conceptions were current, however, of the state of the circulation in 'Secondary Shock', when the Special Investigation Committee began their work. According to Crile (1899), and others who followed his teaching, the condition was due to exhaustion of the vasomotor centre by excessive sensory stimulation. Crile supposed that the low arterial pressure so produced allowed the blood to accumulate in the great veins, and that the output of the heart failed through lack of diastolic filling.

The other conception, which had gained support from several workers in more recent years, also recognized failing output of the heart, through inadequate filling, as the central feature of the circulatory depression, but gave a very different account of its origin.

This other view, starting with Malcolm, and elaborated by Y. Henderson, Mann, and other writers, regarded oligaemia, defect of the volume of blood in effective currency, as the central feature of shock. According to this view, the arteries were constricted rather than dilated in shock, the vasomotor centre attempting to compensate for the reduction in blood volume. This defect of volume was partly, but apparently not wholly due to loss of plasma from the blood, as indicated by an increase of the corpuscular content. Sherrington and Copeman (1893) had described this loss of plasma in shock some years earlier. Mann found that the volume of blood recoverable, by bleeding the shocked animal out through the large arteries and veins, showed a deficiency over and

above that accounted for by concentration. The experience of surgeons and physiologists at clearing stations in France seemed to be definitely in favour of this latter conception, as correctly describing the condition of Shock which they observed, but no adequate theory as to the mode of its causation was available. Henderson had attributed it to acapnia, caused by excessive ventilation of the lungs in response to painful stimuli. The deficiency of carbon dioxide was supposed in some way to reduce the pressure of blood in the veins and thereby retard the diastolic filling of the heart. The Committee could find no evidence of hyperpnoea as a prelude to shock in man; nor did the evidence that lack of CO_2 would retard the circulation seem to be convincing. The claims of acidosis, which was later suggested as a cause of the condition, have been considered and rejected in a previous report of this series (No. 7). No evidence could be obtained of the existence of a nervous mechanism by which such a complex of symptoms could be produced.

In several ways the condition was anomalous. It presented the paradox of arterial constriction associated with low arterial pressure. The low arterial pressure, again, was associated with concentration of the blood, whereas normally the blood takes up fluid from the tissues when the arterial pressure falls. Two of us (D. and L.) had been working for some years on the action of a substance which presented very similar anomalies. This substance was the base 'histamine', which is formed from the amino-acid histidine by removal of CO_2. Its action was interesting not merely on its own account, but as typifying the action of a large class of partial cleavage-products of proteins—products of partial digestion, of bacterial action, &c. Histamine, as also the other substances showing this type of action, had an intense stimulant action on plain muscle, including that of the arteries; yet in the cat, dog, or monkey it caused a fall of arterial blood-pressure, which was certainly not due to action on the heart, but apparently to simple vasodilatation. Injected in larger doses, into the blood-stream of animals of these species, it caused a typical shock-like failure of the circulation, presenting all the features mentioned above—arterial constriction, oligaemia, concentration of the blood, failure of cardiac output. It seemed to us that a more detailed physiological analysis of the condition, which we could thus produce with fair regularity by the use of histamine, would throw light on the hitherto obscure nature of the closely similar condition seen in traumatic shock. A preliminary account of this investigation and of our provisional conclusions therefrom was given in a memorandum issued by the Medical Research Committee in February 1917. Later an added interest has been given to it by the experiments carried out by Professor Bayliss and Colonel Cannon, which have produced direct evidence that substances having this type of action, liberated from injured tissues and absorbed into the circulation, are an important factor in the production of shock. These experiments are described in Memoranda Nos. IV, V, and VI included in this Report. The importance of a factor of this kind is confirmed by

the clinical observations by Major McNee and his co-workers (Memorandum No. VII).

2. Histamine-Shock.[1]

Most of our experiments were made on cats under ether, the arterial blood-pressure being recorded by a manometer connected to a carotid artery. If such an animal receives by a single intravenous injection a dose of 1–2 mgm. of histamine per kilogram of body weight, the effect passes through several phases. There is a preliminary steep fall of arterial pressure, which we have found to be associated with constriction of the pulmonary vessels and over-distension of the right chambers of the heart. This passes in a few seconds, and a second phase appears, in which constriction of the systemic arteries is often sufficient to raise the arterial pressure above its original level. In about thirty seconds this in turn is passing off and the main phase of the effect sets in as a steady, but only moderately rapid decline of the arterial pressure. The respirations during the earlier phases have become accentuated, but as the blood-pressure falls away they gradually become shallower and more widely spaced, until, by the time the pressure has fallen from the initial level of (say) 150 mm. to about 60 mm., they usually fade out altogether. Artificial respiration, immediately applied, does not arrest the downward course of the pressure curve, which usually continues to fall till a level of 40–50 mm. is reached about 4–5 minutes after the injection. If the curve traced by the manometer float is watched carefully during this secondary and lasting decline of the pressure, it is seen that the excursions of the mercury, corresponding with the heart-beats and respiratory undulations, rapidly lose their amplitude, until by the time the pressure has reached a steady minimum the tracing has become an almost unbroken straight line. At first sight one receives the impression that the heart-beat has become feeble almost to extinction. Such a failure of the heart, however, would be difficult to reconcile with the arterial pressure of 40, 50, 60, or even 70 mm. which is still maintained. A hand placed on the chest detects a surprisingly vigorous and regular cardiac impulse. If the chest is opened, under continued artificial respiration, it is seen that the heart is indeed beating strongly and regularly, but that its chambers contain remarkably little blood. Compression of the ventricles between the fingers causes scarcely a movement of the mercury in the arterial manometer. The *venae cavae* in the thorax are seen to be flaccid and half empty, and when the abdomen is opened it is seen that the abdominal *cava* is poorly filled with blood, while the portal vein is flat and almost empty. The arteries, both large and small, similarly contain but little blood, and appear to be constricted rather than dilated. The liver is moderately pale and certainly not distended with blood, and the same is true of the spleen.

[1] A full account of these experiments will shortly appear in the *Journal of Physiology*.

The blood, then, is not in the heart, arteries, or large veins, and no large part of it is accumulated in liver and spleen. What has become of the missing volume, which normally circulates rapidly, filling the heart and great vessels?

An indication of the whereabouts of part of the lost volume is obtained by examining the blood itself. If a drop of blood is taken from an artery before the histamine is given, and another when the shock has become well developed, and the two are compared by haemacytometer, haematocrit, or haemoglobinometer, it will usually be found that the second sample shows a remarkably higher content of red corpuscles than the first. This change is due to passage of part of the plasma out of the blood into the tissues, and the loss in some cases can be shown from haemoglobinometer and haematocrit readings to amount to 50 or even 60 per cent. of the original plasma volume. In the cat about two-thirds of the blood volume usually consists of plasma, so that 60 per cent. of the plasma volume would amount to about 40 per cent. of the whole blood volume.

Changes as great as this in the corpuscular content of the arterial blood are not, however, always seen. In some cases when the histamine is given by a single rapid injection, the loss of plasma, as indicated by the relative volume of corpuscles in the arterial blood, is comparatively slight. This is habitually the case when the histamine is given by continuous slow infusion, so that the dosage is spread over twenty to thirty minutes. In such circumstances the early vasoconstrictor phases of the action are missing, and the pressure undergoes a gradual slow decline, but the state of shock ultimately produced is almost as profound as that following sudden injection of the whole dose. It is highly probable that the capillary blood, if it could be obtained under such conditions, would be found to contain a higher proportion of corpuscles than that in the great vessels, as Cannon and others have observed in traumatic shock. However that may be, the depletion of the blood volume, as shown by the emptiness of the heart and great vessels, is in such cases too great to be accounted for by the demonstrable loss of plasma. By the use of vital red, however, we have been able to demonstrate that, even when the condition of shock is accompanied by but little apparent concentration, a considerable part of the blood has passed out of currency. Thus in one case the directly determined blood volume fell from 160 to 120 c.c., with but a slight rise in corpuscular content (35 per cent. to 39 per cent.).

A process of exclusion led us inevitably to the capillaries in attempting to locate the lost blood, as Cannon (1917), by a similar reasoning, was led to the conclusion that the capillaries must hold the missing blood in traumatic shock. Direct inspection of the internal organs, so far as it gave information, tended to confirm this view. The arterioles supplying blood to the bowel, down to their finest macroscopic branchings, contain but little blood, but the bowel itself shows a diffuse, dusky congestion, and the smallest venules are rendered visible on its surface by their content of dark blood. In the skeletal muscles mere visual examination usually gives little information; but it is certain that a similar accumula-

tion and partial stagnation must occur in them, since the shock can be produced with all its typical features after complete removal of the abdominal viscera. Moreover, if the volume of blood in the animal is increased by transfusion before the shock is produced, the accumulation in the capillaries of the skeletal muscles during the shock becomes very obvious. Shock, as produced by histamine, seemed to us, then, to be a condition in which the circulation failed, and the arterial pressure fell to a low level, in spite of arterial constriction, because the blood drained away into the capillary network and tended to stagnate there, instead of returning to the heart through the veins. And in seeking for an explanation of this condition it seemed to us that, while loss of plasma and consequent thickening of the blood, when they occurred, would accentuate the tendency of the blood thus to accumulate at the periphery, the essential cause must be a general loss of the normal tone of the capillary walls. All observation on the living circulation supports the idea that only a small part of the capillary network is at any one moment functioning as a channel for the blood. With varying needs of the tissues the blood appears to be diverted hither and thither by the closing down of some and the opening up of other channels. We suppose that, under the influence of a large dose of histamine, this capillary tone is lost throughout the body; that the whole of the potentially available capillary channels become simultaneously patent; that the blood percolates into the network of channels as into a sponge. With the rapid diminution of outflow from the tissues into the veins the venous pressure falls, the heart is not filled in diastole, its output rapidly declines, and therewith the arterial pressure. Arterial constriction, while it delays the fall of pressure in the arteries, cuts off only the more effectively the blood in the capillaries from what driving force the depleted heart can furnish.

Such a conception was the only one which seemed to us adequate to account for the unmistakable tendency of the blood to stagnate at the periphery. It involved one assumption, namely that histamine caused loss of capillary tone. If such an action could be proved, it would account not only for the shock-like effect of larger doses of histamine, but possibly also for the evanescent vasodilator fall of arterial pressure which small doses of this powerful stimulant of plain muscle anomalously produced (cf. Dale and Laidlaw, 1910, 1911). This possibility formed the subject of an investigation carried out by two of us (Dale and Richards, 1918), which furnished us with positive evidence in favour of the view that histamine, and by implication the group of substances having the same type of action, owe their effect on the circulation, whether the evanescent depressor effect of small doses or the shock-like effect of large doses, to their power of obliterating the normal tone of the capillaries. It will be obvious how this conception of histamine shock, as due to a poisoning of the capillary endothelium, furnishes also an explanation of the passage of plasma from the blood into the tissues, which characterizes the shock produced by sudden injection of a large dose. The morbid permeability of the capillary walls which this

implies may be regarded as a further stage, produced by a high concentration of the poison, of the effect which in less extreme form is represented by loss of capillary tone.

3. Traumatic Toxaemia.

This sequence of a capillary dilatation, an opening up of channels which under normal conditions have only a potential existence, an abnormal permeability of capillary walls leading to transudation of plasma, and finally a tendency of the blood, thus concentrated by loss of plasma, to stagnate in the widened channels, is already familiar as a local effect. If we observed such a phenomenon occurring in a restricted area of the tissue we should recognize it at once as a mild inflammation. This, as Sollman and Pilcher (1917) have shown, is the effect which histamine produces locally when applied to a lightly scarified area of skin—redness, followed by turgescence, and the formation of a wheal owing to abnormal permeability of the capillaries. A mild mechanical injury, such as the lash of a whip on the skin, will produce a closely similar local effect. Now it has long been recognized that a bacterial poison, which locally causes an intense inflammatory reaction, will produce a profound shock-like collapse of the circulation if rapidly distributed through the system. Histamine, which produces a reaction of inflammatory type when its action is locally restricted, causes a shock-like failure of the circulation when its action is generalized by injection into the blood stream. Analogy, therefore, provides more than one point of support for the suggestion that products liberated from injured tissue, which locally cause an inflammatory reaction like that caused by histamine, would also, like histamine, produce a shock-like condition, if liberated in such quantity as to be rapidly absorbed into the general circulation.

The direct testing of this suggestion, to which our work on the action of histamine had led us, would have been the next step in our investigation, had not our colleagues on the Committee, approaching the problem from a different angle, already provided the necessary demonstration of the occurrence of shock as the result of absorption into the circulation of products from injured tissues. Their results, which are described in other memoranda included in this report, appear to give definite evidence that such a traumatic toxaemia may be at least an important factor in cases of shock. The experiments of Professor Bayliss and Lieut.-Colonel Cannon, as well as the clinical observations reported by the latter and by Major M'Nee, are concerned chiefly with evidence of the liberation of poisons of this class from injured skeletal muscles. At an early stage of the Committee's work Major-General Wallace had called attention to the frequent association of shock with extensive injuries of the muscles. The French surgeons, Delbet and Quenu, who have independently followed a similar line of observation and reasoning, have also directed their attention chiefly to the muscles. In the case of wounds of the extremities, which alone give opportunity for studying the effects of application and release of a tourniquet,

the muscles must obviously be the tissues chiefly concerned. Apart, however, from the extent to which skeletal muscle is involved in war wounds, there seems to be no ground for awarding it a special position as a source of toxic products of injury. Lieut.-Colonel Cannon records the effect obtained by pinching the liver, and it may be well to remember that the contents of the stomach and small intestine provide the richest store in the body of products having this type of action, including some amount of histamine itself. The readiness with which shock is produced by injuries of these viscera and by the leakage of their contents into the peritoneal cavity may be significant in this connexion. The possibility may also be borne in mind that rough handling or undue exposure in operation may weaken the resistance, which the healthy mucosa opposes to the passage into the circulation of toxic constituents from the lumen.

The fact that products are formed in injured tissues, having an action of what we may call the 'histamine type', is of further significance in explaining the progressive nature of the effect. When shock produced by histamine or by traumatic poisons has lasted for some time, the tendency to natural recovery seems to have been lost. If the animal is left to itself, without further administration of histamine, the condition of the circulation continues to deteriorate. We have some evidence to support the view that not only mechanical injury, but lack of oxygen, due to deficient blood supply, will initiate those changes in the tissues which lead to the appearance of substances having an effect of this type. For example, if the blood supply be shut off for some minutes from the hind limbs of a cat, readmission of the blood is followed not only by dilatation of the vessels in these, but also of those in a fore limb, which has been rendered sensitive by denervation to the action of histamine and similarly acting substances. In another part of this report (Mem. No. 2, Bayliss and Cannon) evidence is given of the formation of fixed acids in tissues thus deprived of their circulation (cf. also Wright (1918)). It may be, as has been suggested, that such acids have a similar dilating effect on capillaries, and that their local action may have importance when the circulation has become greatly retarded. It is not difficult, therefore, to understand that the effect of poisons of this type, if sufficiently lasting and severe, tends to perpetuate itself indefinitely. The defective circulation leads to the further formation of substances dilating capillaries, so that the defect is maintained and accentuated. The urgent need for restoring the circulation by appropriate infusion before this vicious circle is closed, and the rapidity with which such a condition may pass beyond the reach of remedy, need no further explanation.

A question of some interest, to which future investigation may possibly find an answer, is whether the condition of capillary dilatation, and the consequent peripheral accumulation of the blood, can be produced by other than chemical agencies. Practically nothing is known of a nervous control of the capillary tone; but it is clear that nervous impulses producing general capillary dilatation,

or the annulment of impulses maintaining a normal capillary tone, if either should be proved to exist, might be as effective in causing shock as the absorption of traumatic poisons. The importance of the chemical factor seems to be demonstrated, but not as yet to the exclusion of other possibilities.

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III. SUPPLEMENTARY NOTE ON HISTAMINE SHOCK

By H. H. DALE, F.R.S.

VARIATIONS in the severity of the shock produced by histamine, and in the tendency of the animal to recover from it, made it clear that other factors than the dose of histamine injected must be concerned in the result. Earlier experiments had suggested that the necessary anaesthetization of the animal, in experiments involving a record of the blood-pressure, was one such factor. Some more recent experiments, made with the direct object of determining the nature and importance of secondary factors, have made this more obvious.

1. EFFECT ON THE NORMAL CAT.

It has been found that relatively large doses of histamine can be slowly run into a vein of an unanaesthetized cat with the production only of mild and evanescent symptoms of depression. The respiration becomes deeper and more rapid, slight cyanosis of the mucous membranes is observed, and the corpuscular content of the blood is somewhat increased during the infusion. These effects, however, rapidly pass off when the infusion is stopped, and the animal soon recovers completely. As much as 10 mgm. per kilogram has thus been administered with only temporary and mild symptoms as the result—a dose many times that which suffices to produce an irreparable condition of shock in the animal under anaesthetic.

2. Effect of Anaesthetics.

The only anaesthetic yet directly studied in this connexion is ether.

A cat, which had some days previously received 10 mgm. of histamine per kilogram without lasting effect, was kept under ether, given on an open mask, for two hours. At the end of this period the arterial blood-pressure was recorded, under continued anaesthesia with ether. It was found to be about 160 mm. (vagi cut); the output of the heart was excellent and the circulation in every way satisfactory. Injection of histamine was then begun. 1 mgm. per kilogram caused a fall of the blood-pressure to 33 mm.; when 2 mgm. per kilogram had been given it had sunk to 26 mm., and the output of the heart was imperceptible on the record. The respiration failed early. Artificial respiration, continued for an hour with pure air, produced no trace of recovery. At the end of this period the heart was still executing regular and fairly powerful beats, but contained hardly any blood. The haemoglobin value of the blood rose from 75 per cent. before to 118 per cent. after injection of histamine. In other experiments the animals were similarly anaesthetized with ether for two hours, and allowed to recover. Histamine was then infused without anaesthetic at different intervals after the termination of the anaesthesia. With an interval of thirty minutes 4 mgm. of histamine per kilogram produced a profound shock, accompanied by great concentration of the blood, the haemoglobin value rising to 146 per cent. and the corpuscular volume by haematocrit to 62 per cent. With an interval of three hours a similar dose caused a shock of intermediate severity, the animal remaining weak and depressed for some hours but recovering completely over night.

3. Effect of Haemorrhage.

The jugular vein of a cat was punctured and blood to the extent of about 40 per cent. of the calculated volume was taken in twenty minutes. The animal was weak immediately after the haemorrhage, but rapidly recovered. Three hours later it showed no definite abnormality. Slow intravenous infusion of histamine was then begun. By the time 3 mgm. per kilogram had been administered the condition of shock was profound and the respiration failed shortly afterwards. Consciousness and reflexes had disappeared earlier. The only sign of life was the continued beating of the heart. Artificial respiration was applied and the blood-pressure recorded. It was found to be 40 mm. and continued to fall slowly to 36 mm. There was no sign of returning reflexes and the animal was killed for examination.

So far as they have proceeded these experiments make it clear, in the first place, that the healthy animal, with unimpaired circulation and normally resistant endothelium, can tolerate relatively very large doses of histamine. No attempt has been made as yet to determine the limit of this tolerance, but a relatively trifling and evanescent effect is produced by doses ten times as great as those

which produce irreparable shock under conditions which render the animal sensitive to this action, though not obviously abnormal in other respects. The mechanism of this tolerance has yet to be investigated. It is probable that the normal, healthy organs can rapidly destroy histamine, and it is possible that anaesthesia or haemorrhage weakens this metabolic defence. On the other hand it can hardly be supposed that the destruction is so rapid that there never exists, during the infusion into the healthy animal, a concentration of histamine which would suffice to determine the appearance of shock in the animal rendered sensitive. Nor is it clear that the liability to the action produced by certain anaesthetics on the one hand, and by haemorrhage on the other, is of the same kind. Such evidence as is yet available is against such a view. A very conspicuous feature of the shock produced by histamine, in the cat subjected to prolonged preliminary anaesthesia with ether, is the rapid concentration of the blood by loss of plasma, and the associated condition of stasis in the capillaries. Most of the experiments on histamine-shock having been made under ether, this phenomenon has naturally figured prominently in the description of the effect. It is fairly safe to assume, therefore, that one factor in the reduced tolerance to histamine produced by ether is a weakened resistance of the capillary endothelium to the poisonous action which renders it abnormally permeable. It should be noted that this weakening, once produced, persists for some time after removal of the anaesthetic. In the one experiment yet made after haemorrhage the loss of plasma was much less conspicuous. The initial haemoglobin value was in this case 86 per cent.; it fell to 60 per cent. as a result of the haemorrhage, and returned only to 74 per cent. after injection of the dose of histamine which proved fatal. The effect of histamine in this case seemed to be largely due to the increased capacity of the vascular system, rendering inadequate for the needs of the circulation a blood volume, which absorption from the tissues after haemorrhage had been inadequate to restore to its normal level, and which loss of plasma after histamine further diminished. As the medullary centres failed from defective blood-supply, this relative inadequacy of volume would be intensified by loss of vasomotor tone. These and other possibilities, however, require further experimental exploration.

Some caution is needed in applying these results to the condition of traumatic shock. At several points it is uncertain how far the analogy will hold. For example, there is no evidence which will enable us to compare histamine with the toxic substances produced by trauma, with respect to the rapidity of their destruction by healthy organs normally supplied with blood. We cannot safely assume that the otherwise healthy organism would show the same tolerance for these traumatic toxins as it does for histamine. At the same time it must be remembered that all the experimental evidence concerning the production of shock by extensive tissue injury has been obtained, and must in the nature of the case be obtained, by experiments on animals continually anaesthetized with substances such as ether or urethane, or subjected to preliminary

decerebration. It seems in the highest degree probable that the sensitiveness of the animals to traumatic toxins has been thereby greatly enhanced.

The analogy with the experience of military surgeons, again, can hardly be missed. The special liability to shock of patients whose wounds have been complicated by severe haemorrhage is almost a truism. It seems to us, however, that a clear cut demonstration of the fact that a toxaemia, of trifling significance to the normal animal, may prove rapidly fatal when it follows some hours after a severe, but not in itself dangerous haemorrhage, may throw light on the incidence of shock in wounded men, when apparently on the way to recovery from the immediate effects of a haemorrhage. There is a suggestive analogy, again, between the greatly increased liability to histamine shock produced by ether, and the experience that patients, who were previously in moderately good condition, may pass into a dangerous condition of shock after the administration of anaesthetics of this class for the purpose of a necessary operation. The fact that anaesthesia with nitrous oxide and oxygen is practically free from this danger arouses the expectation that it will prove to have little or no sensitizing action for the effect of histamine. This, however, is one of many points still awaiting investigation.[1]

The results of these experiments do not, in our opinion, weaken the evidence in favour of regarding traumatic toxaemia as a factor of primary significance in wound shock. They emphasize, however, the essential complexity of the condition, and suggest that a clearer conception may result from further investigation of contributory factors.

[1] Since the above was written, actual experiment has shown that a cat under anaesthesia with nitrous oxide and oxygen can tolerate the infusion of 10 mgm. of histamine per kilogram, with effects little if at all more severe than those produced in the unanaesthetized animal. This is the case even when the anaesthesia is maintained for an hour before the histamine is administered. In one such case the cat on a subsequent day was anaesthetized for an hour with ether, after which 2 mgm. of histamine per kilogram produced fatal shock.

IV. NOTE ON MUSCLE INJURY IN RELATION TO SHOCK

By Lieutenant-Colonel W. B. Cannon, M.R.C. (U.S.A.), and W. M. Bayliss, F.R.S.

Evidence having been accumulating from various directions that injury and destruction of tissues are potent causes in producing a state of low blood pressure and 'shock', we made experiments[1] on cats to investigate the effects of injury to muscles. The chief interest of the results obtained lies in the demonstration that they are not due to nervous reflexes but to the absorption of some toxic substances given off by the injured tissues.

1. The Experimental Production of a State of Low Blood Pressure by Injury of Muscles.

The flexor group of muscles in the thighs of the cat were used. We placed an iron block at one side of the thigh in animals under urethane, and, with the flat head of a hammer weighing about one pound, we struck these muscles six or seven times, so that they were ruptured and severely bruised. The skin was rarely broken by the blows. In a few instances the femur was fractured, but this had no consequence different from that resulting from muscle injury alone.[2] As time passed after the traumatization, the muscles underwent much swelling; and at autopsy there we found varying amounts of extravasated blood. In no case, however, was there sufficient bleeding into the wounds to account, by itself alone, for the effects observed. The effects are illustrated in Fig. 1. The blood-pressure as a rule falls sharply during the traumatization. This fall is followed sometimes by a slight temporary rise, as in Fig. 1. The pressure then continues at a fairly even level for a time, and then a secondary fall occurs.[3]

The promptness of the first fall suggested that it was reflex in nature. It occurred, however, after the cord had been cut in the upper lumbar region; in fact, it appeared to be more pronounced, but this may have been accidental. It failed to appear if the aorta was clipped above the iliacs during the traumatization, although the nerve conduction would not be impaired during this short anaemia.

[1] A brief description of these experiments was given at the meeting of the Medical Research Society of the American Red Cross in Paris, March 15, 1918, and published in the *Medical Bulletin* of the Society, April, 1918, p. 426.

[2] Porter (1) has declared that shock occurs mainly in cases of fractured femur or multiple wounds of subcutaneous tissue. He ascribes shock to the effects of fat thus brought into the circulation—an inference for which there exists as yet very little evidence. In our experimental cases, there was no noteworthy amount of subcutaneous fat, and examination of the lungs after death revealed no indication of pulmonary emboli.

[3] The amount of blood taken for determining the CO_2 capacity was about 3 c.c. each time. The animal which served for the experiment recorded in Fig. 1 weighed 2·5 kilos. and had an estimated blood volume of 150 c.c.

Furthermore, there was no change in the alkali reserve between samples taken just before the injury and at the time of the sharp fall of pressure. The observations indicate that the sharp fall is not due to any general effect of the trauma on the circulation brought about through nervous agencies or liberated acid. It may be due to a combination of dilatation of blood vessels in the injured area, together with some extravasation of blood, with the rapid setting free of a chemical substance acting as a powerful depressant on the blood-pressure.

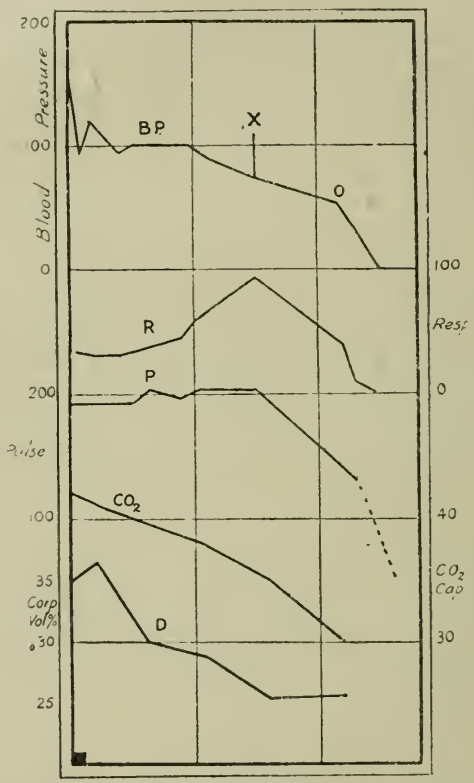

Fig. 1. Record of changes in the blood-pressure, respiration, pulse and CO_2 capacity of the plasma after injury of the flexor muscles in the thigh. At X, asphyxia caused the rise of blood-pressure indicated. Urethane anaesthesia. At O, no rise in asphyxia.

The secondary fall may be explained by the continued absorption of the depressant substance and by the establishment of a vicious circle in consequence of the low blood-pressure. This, as would be expected from Araki's experiments on the production of lactic acid when the blood supply is defective, is associated with a steady fall in the bicarbonate reserve of the blood.

A remarkable effect on the respiration is usually to be seen. The rate increases greatly, from a normal of about 30 per minute to as much as 180. The depth is shallow. As the state of the animal becomes worse, the rate decreases steadily until death. The rate of

the pulse follows a similar course. *Post-mortem*, the appearance of the muscles injured reminded us strikingly of the shell wounds which we had seen in France, particularly if the conditions at similar times after the infliction of the injury were compared.

2. Muscle Injury in Cases of Shock in Man.

The nature of the wounds typically seen in cases of wound shock may be judged from the following records made by one of us at a casualty clearing station where only the most severely wounded men were admitted. Some of them were seen by both of us. In reading these records it should be understood that the wounds were often made by large, jagged pieces of shell moving at high velocity. When such a missile breaks the humerus, or the femur, or the ilium, it smashes and tears extensively the overlying muscles, which, in the thigh and hip, form a thick layer. In all the cases there was shock, accompanied by acidosis.

E. G. Compound fracture of left ulna and radius, arm nearly severed, wounds of right arm and left side, abdomen opened, intestine and omentum protruding.

C. P. H. Shell wounds of right thigh, with fracture of the femur, and of left arm with fracture of the humerus, wounds of the face.

G. D. Wounds of the left arm with fracture, left leg with fracture, flesh wounds of the right thigh and abdomen.

G. J. H. H. Shell wounds of right ankle, of left leg with fracture, and of the muscles of the buttock.

H. J. H. Bursting shell broke right femur, left tibia and fibula, and injured right arm.

A. J. R. Extensive wounds of both legs, left foot and left arm.

W. G. Wounds of buttock with fracture of ilium, also wounds of right foot.

P. K. Fracture of left femur (much comminuted) and right tibia.

W. A. T. Wounds of buttock and perinaeum, muscles below the buttock torn across and smashed in both legs.

G. K. Wounds of both arms, left thigh, left foot, compound fracture of the right thigh.

R. C. Compound fracture of right femur, multiple shell wounds, left femur, buttock and chest.

A. H. Multiple shell wounds. Large wound of the left loin involving the gluteal muscles, fracture of pelvis, extensive wound of right calf muscles and the muscles of the left thigh and left calf, and numerous wounds in back and chest.

It is obvious that with such wounds as these large amounts of muscle would be torn and smashed. And, just as in the animal experiments recorded above, the injured muscle would produce metabolites, which, on being absorbed into the blood stream, would indicate their presence by a decrease in the blood-pressure, with other signs of shock.

3. The Experimental Production of Low Blood-Pressure by Temporary Exclusion of the Circulation from the Legs.

Certain products are known to be given off by muscles when the oxygen supply is diminished or cut off. To determine what effects these have on the circulation, we placed a small clip on the aorta immediately above the iliac branches, in a cat under urethane. The clip was left in position for 62 minutes. The average blood-pressure during this period was 138 mm. Hg., and the CO_2 capacity was about 43 per cent. (see Fig. 2). The removal of the clip was

followed by a drop in the blood-pressure to 65 mm., and a fall in the CO_2 capacity of the plasma to 32 per cent. In about 20 minutes the blood-pressure had risen to 82 mm., and the CO_2 capacity to 38 per cent. For 45 minutes thereafter the blood-pressure did not alter, but there was a slight rise in the alkali reserve (2 per cent.).

This experiment shows that the material swept out of a muscular portion of the body by the returning blood contains various metabolites which lower the blood-pressure. (See Vincent and Sheen, 2.) Amongst these is lactic acid, as shown by the reduction of the carbon dioxide capacity of the plasma, which was reduced by 11 volumes per cent.

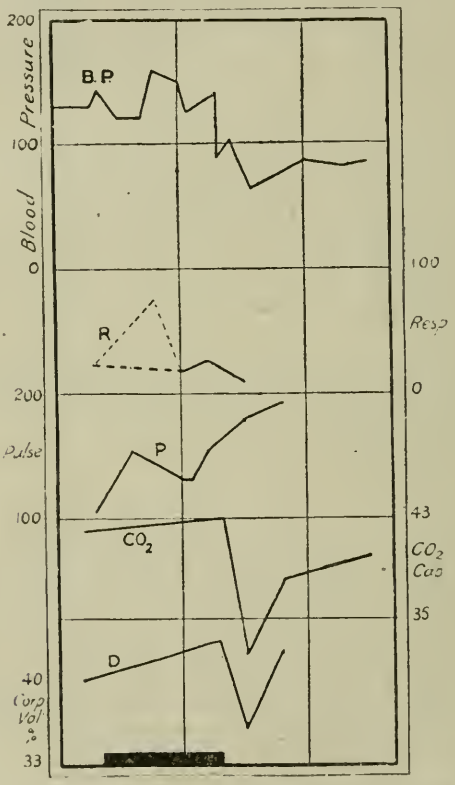

Fig. 2. Record of blood-pressure and CO_2 capacity during and after the exclusion of the blood supply to the hind legs. Cat under urethane. The aorta was clipped just above the iliac branches from 10·21 to 11·23.

In connexion with the facts given above, it is of interest to note that massage of damaged muscles, unless a nerve happens to be pinched, results in a further fall of blood-pressure. The phenomenon has probably some significance in relation to the increase of shock produced in cases of fracture of the femur when the limb is not adequately supported during transit to the casualty clearing station.

Besides the general effects of the temporary anaemia of a portion of the body on the remainder of the body, it is probable that there are additional local effects. It is well known that local dilatation of all vessels occurs in consequence of temporary exclusion of blood from a part—a phenomenon which has been ascribed to the chemical changes resulting from inadequate oxygen supply (Roy and Brown, 3). This dilatation would augment the influence of the circulating metabolites in lowering blood-pressure. In this connexion, recent testimony of Erlanger and his collaborators (4), that temporary exclusion of the circulation from any considerable portion of the body results in shock, is of interest, for the changes described above would in any such case come into play.

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V. FURTHER OBSERVATIONS ON THE RESULTS OF MUSCLE INJURY AND THEIR TREATMENT

By W. M. Bayliss, F.R.S.

The experiments described in the preceding note were continued, after Major Cannon's departure for France, with especial reference to the most appropriate mode of treatment of the state produced. The interest of this form of experimental shock is that it appears to correspond more closely with that met with in wounded men than most other forms produced in the laboratory do.

1. Concentration of Blood.

There is one to which I may refer briefly before proceeding to the new experiments. This point is obvious from the records of the experiments made by Cannon and myself, although it was not mentioned in the previous note. It was remarked that the actual amount of extravasation of blood was not great, but that there was a marked swelling of the legs, doubtless resulting from fluid escaped from the blood vessels. There was, also, in most cases, especially in the early stages, a noticeable increase in the corpuscular concentration of the blood, although this was sometimes masked by the dilution due to the low blood-pressure.

2. Effect of Haemorrhage.

In repeating the experiments, I found that serious secondary shock could not always be produced. Strong, healthy cats were able to resist the effects of the injury and the blood-pressure,

which was more or less depressed as an immediate result of the injury, rose again almost to normal after a variable period of time. But, if a comparatively small amount of blood was removed, say about 15 per cent. of the blood volume, at a time when recovery appeared to have taken place, secondary shock could always be brought about. The loss of this amount of blood is rapidly recovered from by the uninjured cat.

3. The Nature of the Depressant Substance.

The fact that the primary fall of pressure is not accompanied by decrease of bicarbonate reserve suggests that lactic acid is not the responsible agent. That there is a progressive production of acid in the course of the secondary fall is easily accounted for by the low blood-pressure itself.

There are, moreover, many reasons, discussed in another report, which show that 'acidosis' in itself is not a serious factor. Further, experimental test proves that the injection of lactic acid during the state of shock from muscle injury does not in any way exaggerate the state, and in some cases has been found to benefit it by raising the blood-pressure. The intravenous injection of solutions of sodium bicarbonate, on the other hand, have merely a very brief effect in raising the blood-pressure, and, if repeated small doses are given during the development of the shock, they have no power to prevent its appearance.

If extracts of muscle are made by boiling with 0·9 per cent. sodium chloride solution, they contain lactic acid, as is well known. If injected intravenously, while a plethysmographic tracing of the volume of the intestine is being taken, a fall of blood-pressure, together with dilatation of the intestinal vessels, is observed. But the effect is precisely the same in degree if the extracts are previously neutralized.

Lactic acid, therefore, is not the active agent, nor other acids *quâ* acids. Some other substance produced by tissue disintegration must be responsible, and we naturally think of histamine, or related compounds, whose action has been investigated by Dale, Laidlaw, and Richards.

Massage of the injured muscle causes a fall of blood-pressure, which is frequently permanent. This is associated with a dilatation of the intestinal blood vessels, and is, no doubt, due to an increased rate of diffusion of the toxic products into the blood stream.

4. Effect of Gum Solutions.

Although the intravenous injection of gum-saline had shown itself to be very effective in replacing blood lost by haemorrhage, I did not feel sanguine that it would prove of value in low blood-pressure from other causes. The fact that when the blood vessels are deprived of the influence of the vasomotor centre, no kind of intravenous injection is effective for more than about five minutes, not even blood, cast doubt on the probability of gum being of use in

low blood-pressure from causes other than loss of blood. On the other hand, if the view that there is a capillary dilatation and stasis of blood in wound shock is correct, the blood may be looked upon as being as effectively out of circulation as if lost to the outside, and it might possibly be replaced, at all events until the normal capillary circulation is restored, by an addition to the volume of the blood.

On testing the question experimentally in cats, I found that the blood-pressure could be permanently restored by gum-saline, with the disappearance of the other signs of shock. Further, the development of shock from even very severe injuries could be prevented by repeated small injections of gum as the blood-pressure fell from time to time. It is also quite effective as late as five and a half hours after the injury, provided that the blood-pressure has not been so low as to cause paralysis of the nerve centres.

It appears that the conclusion must be drawn that the toxic products can be removed, or destroyed, as quickly as they pass into the blood current, if the volume of the blood is kept sufficiently large to ensure a good circulation and supply of oxygen to the tissues. Whether the toxic products are oxidized, as lactic acid is, or rendered harmless by passing through the liver, is a matter for further investigation. We know that histamine disappears very rapidly if the circulation is effective.

It may be remarked that Fraser and Cowell and Drummond and Taylor report cases of wound shock, in which there was no evidence of much haemorrhage, permanently restored by gum-saline.

The concentration of the blood after muscle injury, referred to above, might suggest that 6 per cent. is too high a concentration of gum to use in cases of shock from injury of tissues. It is not clear why it is the case, but in practice 6 per cent. is more effective than a lower concentration. Perhaps, the lower strengths, owing to lack of the optimal colloidal osmotic pressure, lose water to the tissues and hence become merely equivalent to an ineffectively small quantity of the higher concentration. It is apparently feared that the heart may be overloaded, but evidence shows the strength of the cardiac contractions has not suffered in consequence of the state of shock. One fact that shows this is the capacity of the heart to maintain permanently a high arterial pressure as soon as it is given enough blood to put into circulation.

The amount necessary to inject in these experimental cases can only be discovered by trial. If the first injection is only partially successful, a further one is usually effective. When the muscle injury is combined with haemorrhage, it is found that a much larger volume of gum-saline is required than corresponds to that of the blood removed.

5. The Effect on Respiration.

The rapid, shallow respiration referred to in the preceding paper is, apparently, an aspect of that form of respiration ascribed by Haldane to an exaggeration of the Hering-Breuer inhibition of

inspiration. In the case before us, the effect is probably due to a commencing deleterious action of the low blood-pressure on the respiratory centre. Its disappearance when gum is injected is remarkably sudden; the normal respiration returns before the blood-pressure has risen to any great extent.

It should be noted that this form of respiration is not that of an increased acidity of the blood, where there is always an *increase* in depth, but not always in rate. The respiratory effect of releasing a clamp on the abdominal aorta, after an hour of deficient blood supply to the hind-legs, is similar to that of increased hydrogen-ion concentration. The fact suggests that the effect of injury to the muscular tissue is to give rise to products of a different kind from those resulting from mere anaemia.

As the nerve centres become more affected by the duration of the low blood supply, the rapid respiration gives place to one becoming slower and gradually more shallow.

6. Final Paralysis of Nerve Centres.

In the cat, both the respiratory and the vasomotor centres lose their excitability before death finally occurs. At this paralytic stage, no intravenous injection, whether of blood or of gum, is of avail, unless the stage of paralysis has only just come on. Microscopic investigations made by Colonel Mott show that there are degenerative changes in the nerve cells, like those which appear when the brain has been anaemic for some time.

It is, naturally, impossible in the case of the wounded man to know whether the irrecoverable stage has been reached, and it is an incidental advantage of gum solutions that there is no need to exercise economy in their use, even in such cases as appear quite hopeless. The results, however, cannot be regarded as valid tests of the efficacy of either blood transfusion or gum injection. It is, of course, unnecessary to remark that, in a matter of life and death, no question of rivalry of modes of treatment will be allowed into consideration. Blood would reasonably be preferred, if available. But, in times of stress, the injection of gum solution is a simpler matter and there should be no limit to the supply. It is, I venture to think, a matter of some satisfaction that a substitute for blood, as effective as gum-saline has shown itself to be, can be provided.

VI. SOME CHARACTERISTICS OF SHOCK INDUCED BY TISSUE INJURY

By Lieutenant-Colonel W. B. Cannon, M.R.C., U.S.A.

The following experiments, continuing those begun in co-operation with Professor Bayliss, were performed in the Laboratory of Surgical Research of the American Expeditionary Forces in France. The earlier experiments were made under urethrane anaesthesia. In the present series light ether anaesthesia was employed, and the amount of ether given was reduced as the state of shock developed. In addition to cats, dogs and rabbits were used. Muscles of the thigh were injured, in some cases by hammering and in others by crushing with heavy pincers. It was found also that pinching the tips of the lobes of the liver induced a fall of pressure with no evidence of splanchnic congestion.

The initial fall of pressure observed in the earlier experiments immediately after muscles were hammered was often not seen when muscles were crushed in pincers (see Fig. 1). The initial fall, therefore, is not an essential feature in the establishment of shock pressure. In a series of cases the average time elapsing between injury and the beginning of the fall of pressure was eighteen minutes, with variations between thirteen and twenty-five.

The development of a low blood-pressure after muscle injury was proved not to be due to loss of fluid from the systemic circulation, by carefully skinning the posterior extremities after death, disarticulating the legs at the knee and removing the thighs at the hip by symmetrical cuts through the tissues; the thighs were then weighed. The difference in weight was as low as 11 per cent. of the estimated weight of the blood of the animal—an amount which the animal could readily lose without any fall of blood-pressure whatever.

That the 'shock' was not due to nervous stimulation was confirmed not only by obtaining, after previous severance of the cord in the lumbar region, the usual fall of pressure from trauma; but also in other cases after previous severance of the nerves to the limb at the point of their emergence from the pelvis (see Fig. 3). Furthermore, the shock was not produced when the nerves were intact but the blood vessels tied (see Fig. 2).

The experiment just mentioned (Fig. 2) indicated clearly that some substance given off from the injured tissue was the cause of the drop in pressure, for the permanent fall occurred only when the blood was permitted to flow in and out of the damaged region, thirty-three minutes after the traumatism.

If, after a low pressure has become established in consequence of muscle trauma, the blood vessels of the injured leg are tied, the pressure may soon begin to rise, and may continue until the original

Fig. 1. Typical fall of blood-pressure after crushing muscles of thigh with pincers.

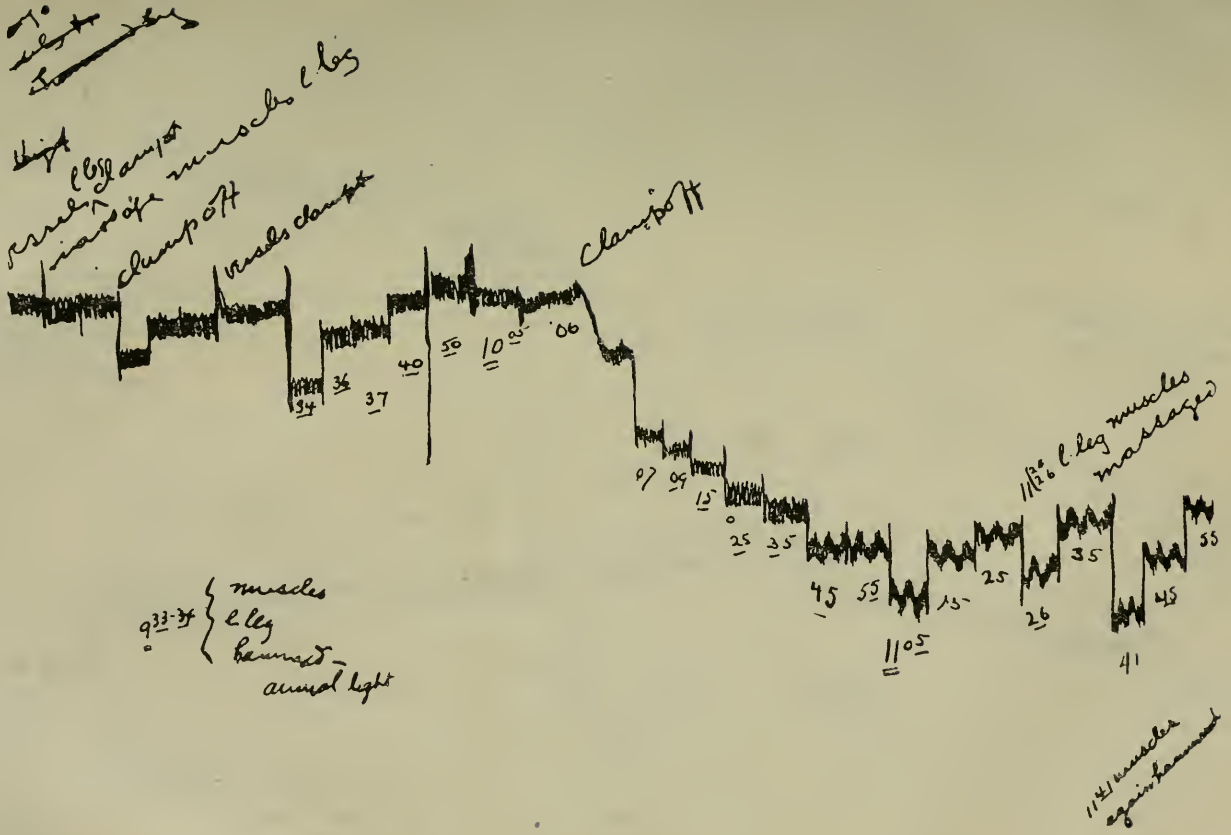

FIG. 2. Failure of blood-pressure to fall at the usual time after muscle injury if the blood vessels to the injured region were tied. On restoration of the blood flow, pressure promptly fell.

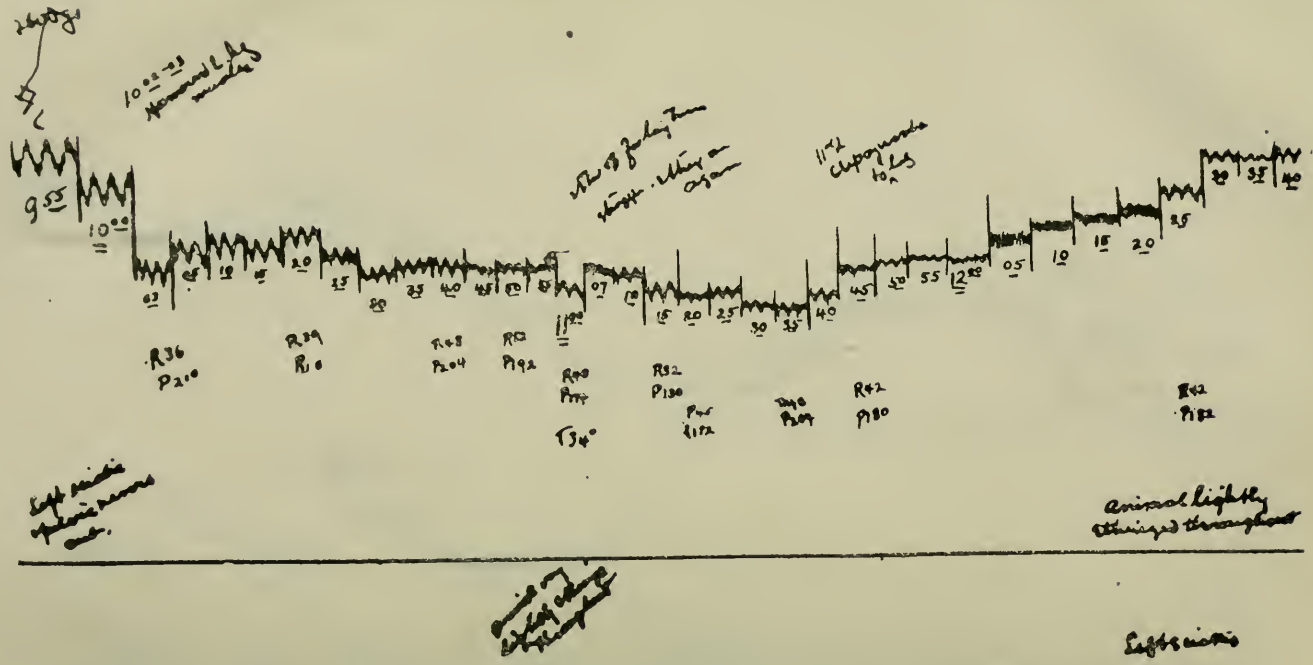

Fig. 8. Rise of blood-pressure to original level after tying vessels to injured region. In this case the nerves of the injured leg had been cut.

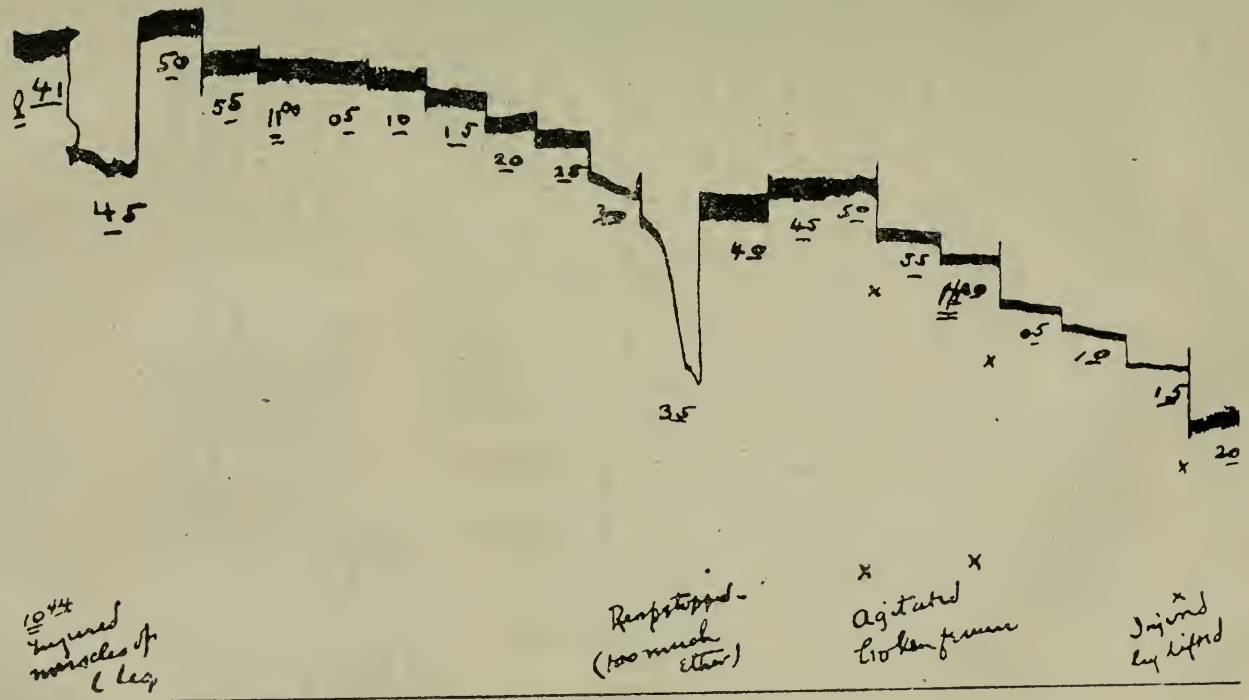

Fig. 4. Rapid induction of shock pressure through agitation of broken femur.

pressure is re-established (see Fig. 3). If the tissue damage has not been too great, the pressure may fall to less than 100 mm. of mercury, and then spontaneously rise to the former level. This result seems to indicate that the toxic material is limited by the amount of injury, and that after it has produced its depressant effect the pressure rises because no more of the material is being produced.

In a number of instances in which the femur was broken, the lungs were examined carefully for evidence of fat, without success. The shock, therefore, produced in these cases was not complicated by pulmonary fat embolism.

Further, if in case of muscle injury the femur was broken, the fall of pressure was accelerated by agitation of the broken bone in the tissue (see Fig. 4). This observation is significant in relation to the benefits which are derived from carefully splinting broken limbs during transport.

On the assumption that the substances given off from injured tissue were products of autolysis, and that autolysis occurs when tissues become acid, it was thought that there might be advantage obtained by a high alkali content of the blood. Twenty-three c.c. of half normal sodium bicarbonate were given by stomach to a cat weighing 2·8 k. The CO_2 content of the plasma a half-hour later was 50 vols. per cent. The muscles were then crushed. An hour later the pressure had fallen 60 mm. of mercury, though the CO_2 content was still high, 49 vols. per cent.

That the alkali reserve diminishes as the blood-pressure falls to a shock level was confirmed in a number of instances. Studies of the respiratory exchange in animals before and after the establishment of a shock blood-pressure, made by Lieutenant J. C. Aub, have revealed a very pronounced decrease of metabolism. In some instances a fall of pressure to 60 mm. of mercury has resulted in a reduction of the calculated heat output by more than 50 per cent. From these figures, it is clear that shocked individuals not only lose heat rapidly by sweating, but fail to produce sufficient heat to keep themselves warm.

In confirmation of Bayliss's observations, it has been found that gum salt solution can cause, early in the shock resulting from muscle injury, a sustained rise of blood-pressure, and that further injections will result in further rise. If, however, a shock pressure is permitted to continue until bulbar centres are damaged, as indicated, e.g. by respiratory irregularities, the injection of gum salt solution has only temporary value in restoring pressure.

VII. OBSERVATIONS ON WOUND SHOCK, ESPECIALLY WITH REGARD TO DAMAGE OF MUSCLE

By Major J. W. McNee, Captain A. F. Sladden, and Captain J. E. McCartney, Royal Army Medical Corps.

During a period of heavy fighting in April and May, 1918, an opportunity was afforded of carrying out resuscitation work in a Casualty Clearing Station, during the greater part of the active operations. At this time the hospital zone had been withdrawn to a considerable distance from the line, increasing the journey of the wounded man and lengthening the period between wounding and admission to hospital. As a result of these circumstances, many men arrived in a severe state of wound shock.

In this report no attempt will be made to give a complete account of the observations made; it is only desired to give prominence to a few points which may be of importance.

It may be stated at once that it was generally quite impossible to determine with certainty, when a case was admitted, whether the man was suffering from haemorrhage alone or from shock in addition. It was only by watching the effects of treatment that the predominance of one factor over the other could be established. Moreover, in considering the lines of treatment available for resuscitation, it soon became obvious that, judging by results, only three methods produced any real effect. These methods were calculated to benefit three phenomena common to all men suffering from the various degrees of wound shock and haemorrhage, namely:

1. Lowering of the body temperature.
2. Lowering of the blood-pressure.
3. Diminution of the blood volume. (Cf. N. M. Keith, Mem. No. VIII of this Report.)

Of these, the two last would appear to be dependent on one another.

Lowering of the body temperature was combatted by various methods of rechauffement, and also by giving the infusions noted below at a temperature above normal body heat.

The lowered blood-pressure and diminished blood volume were treated by either gum-salt infusions, or by transfusion of citrated blood by the Robertson method. In passing, we may state as our experience that the effects of gum-salt infusion and blood transfusion seemed essentially the same, and certainly among the cases none which had failed to respond to gum infusion reacted later to the transfusion of blood.

The infusion of gum solution does not, to a superficial observer, yield nearly the same immediate dramatic effects as are often obtained by blood transfusion. With blood, the man loses his ashen colour, the face and lips redden, and the man's general appearance alters completely. Nevertheless, such a man may quickly sink and die, in spite of his apparent resurrection for the moment. With

gum solution, red corpuscles being absent, no dramatic change in colour results, and the observer must look deeper than the skin for evidences of improvement. Above all, he must watch the blood-pressure.

We would submit then, that in the present state of our knowledge, the phenomena of cold, lowered blood-pressure, and diminished blood volume, form the sole symptom complex amenable to treatment in the cases admitted to a resuscitation ward.

It is evident that in cases suffering from haemorrhage alone, unaccompanied by shock, the symptom complex noted above is conspicuously present. We believe, indeed, that in the resuscitation ward it is the cases of haemorrhage combined with not more than a very moderate degree of shock which constitute the successes. This point has already been sufficiently suggested in the memorandum written by Drummond and Taylor.

We have attempted, as have many other observers, to combat a further phenomenon present in shock, namely, the occurrence of acidosis. All that can be stated is that in our hands the administration of sodium bicarbonate has never resulted in any apparent benefit to the case.

When all the deaths from gross anatomical lesions, and all the cases in which methods of resuscitation are successful, were accounted for, we were left with a considerable number of men who, in spite of all treatment, went steadily downhill and died. We came to regard these cases, which formed more than two-fifths of those admitted to the resuscitation ward, as the true examples of wound shock. It is these cases which merit the closest study, with regard to aetiology and possible methods of treatment. Autopsies were made on a number of such cases very soon after death, and the wounds carefully examined for evidence of microbic infection. In this way, one suggestion which has been madewith regard to causation has been negatived, since it was established that no extensive bacterial infection existed in the wounds at death. (The brains, &c. from some of the men examined, were sent to Col. Mott for histological examination. His results are reported in Mem. No. IX.)

There was one finding, however, which was so striking as to suggest that it might have some bearing on the production of the state of shock, namely the frequency with which *extensive injury of muscle tissue* was present in the severe and fatal cases. Several instances, ending fatally, were observed of small multiple bomb wounds, which collectively had caused great laceration of muscle, but where neither bone nor any vital structure had been touched. Bacterial infection, moreover, was shown to be unimportant in these wounds. In cases of compound fracture, which are notoriously liable to shock, extensive damage of muscle is of course invariably present.

The cases considered to be true wound shock died, in the majority of instances, without the least attempt at rallying, even after treatment by blood or gum transfusion and other methods of resuscitation. Some, however, showed a temporary improvement, but then

rapidly sank again. Where the wound consisted of a severe laceration of a limb it was sometimes possible, by watching for the height of the improvement, to perform a very rapid 'guillotine' amputation of the limb under gas and oxygen anaesthesia. Such an operation was commonly followed by a remarkable and maintained improvement, so rapid and striking as to appear a direct sequel to the removal of the damaged limb. In one case, where the patient was too shocked to allow of any movement whatever, a similar good result was obtained by tying a tourniquet as tightly as possible round a limb so badly smashed that amputation was seen to be inevitable if the patient survived. Resuscitative methods were then proceeded with, and amputation carried out later.

A short series of cases, illustrating points referred to in this report, is given below.

Case 1. *An example of severe haemorrhage, not complicated by much shock. Rapid recovery after gum-salt infusion.*

Pte. M., 21st West Yorks. Shell wounds of both thighs. Severe haemorrhage noted on admission at midnight. Taken straight to the operating theatre, in a pulseless condition, and very cold. Infused with 6 per cent. gum-salt solution during operation, at which the profunda femoris artery was found bleeding and was ligated. Pulse improved quickly after infusion, and the patient made a good recovery.

Case 2. *An example of very severe secondary haemorrhage, uncomplicated by shock. Rapid recovery after gum-salt infusion.*

Lieut. S., 8th K. O. R. Lancs. Admitted with a shell wound of the elbow joint. Operated on at once, and elbow joint excised. Appeared to be doing well, but suddenly during the night had a severe secondary haemorrhage, and was found pulseless and almost dead. Bleeding stopped by pressure, and gum-salt infusion given. The pulse returned at once, and the patient made a rapid and complete recovery.

All the cases recorded below presented extensive laceration of muscle, without injury to bones or to any vital structure or organ. All ended fatally with the exception of case 8.

Case 3. Pte. R., 1st Black Watch. Multiple small bomb wounds of left thigh, left leg, right shoulder, &c. No injury to bone. Pulseless and cold. Infused with 500 c.c. of gum-salt solution, but never rallied. Died six hours after admission.

Case 4. Pte. R., 4th Royal Fusiliers. Multiple bomb wounds of left arm, right thigh, right leg, and right foot. No bone injury. Infused with gum-salt solution soon after admission, but remained pulseless. Transfused with blood four hours later, but showed only a very transient reaction. Died rapidly.

Case 5. Pte. B., 11th Manchesters. Shell wounds of left pectoral region, and of right deltoid muscle. No injury to bone. Operated on at once, and wounds partially cleaned. Condition grave, and gum-salt infusion given. Slight temporary improvement resulted. One hour later, 600 c.c. of blood transfused. Death occurred in a few hours.

Case 6. Sergt. D., 1st Northumberland Fusiliers. Shell wounds of scrotum, left buttock, and front of left thigh. Pulseless and very cold on admission. Warmed, and infused with 750 c.c. of gum-salt solution. Very slight temporary improvement, but death occurred six hours after admission.

Case 7. Pte. M., 1st Northumberland Fusiliers. Shell wounds of right arm and left thigh, No bony injury. Pulseless, cold, and vomiting on admission. Infused with 600 c.c. of gum-salt solution, and showed a temporary improvement. Relapsed later, and became profoundly shocked. Transfused with 400 c.c. of blood, but died fourteen hours after admission.

Case 8. *A case in which removal of a lacerated limb was followed by rapid improvement.*

Pte. C., 1st Rifle Brigade. Admitted with a severe wound above the knee, causing extensive injury to muscle. Pulseless and pallid. Infused with gum-salt solution three hours after admission, and warmed. Condition improved slightly, and a quick 'guillotine' amputation through the thigh was performed eight hours after admission. Thereafter improvement was immediate and maintained. The patient was evacuated to the Base, doing well.

Summary and Conclusions.

1. In resuscitation work the treatment of three phenomena has alone yielded successful results, namely:

(*a*) Lowering of the body temperature.

(*b*) Lowering of the blood-pressure.

(*c*) Diminution of the blood volume.

2. The treatment of acidosis by administration of sodium bicarbonate has not been found of practical value in cases of shock.

3. It is the cases of haemorrhage, combined with little shock, which form the successes in resuscitation work.

4. Cases exhibiting the severer degrees of shock die in spite of all the methods of treatment at our disposal.

5. A number of men suffering from pure muscle injuries, without damage to bone, have been seen to die apparently of shock. It has been established that microbic infection is not an important factor in these cases.

6. It is suggested that absorption of some product from the damaged muscles may have some aetiological importance in these fatalities. In favour of such a view is the great improvement which may follow a rapid amputation of a lacerated limb.

7. Muscle damage could not be more than one of a group of the unknown causes of wound shock. The suggestion is chiefly made as one easily amenable to experimental investigation.

Our thanks are due to Major-General Cuthbert Wallace, C.B., C.M.G., and Lieut.-Colonel Spurgeon Campbell, C.A.M.C., for the opportunity given to study and treat the cases dealt with in this report.

VIII. BLOOD VOLUME IN WOUND SHOCK

By Captain N. M. Keith, R.A.M.C.

1. Introductory.

The problem of early effective treatment of soldiers suffering from wound shock presents many difficulties. This is largely due to the fact that the causative agent or agents are still obscure, and that many possible factors may contribute to the development of the pathological condition. The relative significance of these contributory factors is of special importance from the preventive and therapeutic standpoint. Severe wound shock has a definite relationship to the nature of the original trauma and the loss of blood. Exposure to cold, inability to assimilate fluid, and early wound infection are also secondary factors that aggravate the primary condition of shock. Preventive measures can largely eliminate the effect of exposure, while early transfusion will supply the blood lost. Various infusions will give the much-needed fluid, and an infection, particularly in the limbs, can be eliminated by appropriate surgical treatment. Still there remain cases in which, after such

care and treatment, the shock condition threatens the patient's life. In view of these facts, and in order to establish certain points for further therapeutic attack, the characteristic clinical symptoms of shock are now briefly outlined.

Wounded soldiers suffering from shock on arrival at the C.C.S. present such characteristic symptoms that with some experience the condition can be recognized almost at a glance. The peculiar grey colour of the face, the cold extremities and the tendency to be restless make a striking clinical picture. Though critically ill, the soldier is mentally extremely alert, and invariably asks for a drink in order to quench his insatiable thirst. Unfortunately if water is administered, vomiting soon results. Dyspnoea is rarely a troublesome symptom, owing in part to the previous liberal use of morphia, but general restlessness is often most marked and difficult to control. On further examination one finds the pulse weak and rapid and the blood-pressure lowered. In some cases, however, of severe shock the blood-pressure may be but little lowered although the pulse is thready and rapid. The closely associated symptoms of pallor, thirst, and a rapid weak pulse immediately suggest some fundamental circulatory disturbance. The object of the present investigation was to determine as accurately as possible the actual condition of the circulation in men presenting clinical symptoms of wound shock and observe the response to the treatment instituted.

2. Blood Studies.

Crile and Cannon have pointed out that acidosis is met with in shock. In the present series of cases determinations of the CO_2 content of the plasma by the Van Slyke method (1) demonstrated that often a slight reduction in the reserve alkalinity was present; but this reduction never reached the level at which symptoms due to acidosis might be expected to arise. On the other hand, in cases of wound shock complicated by gas gangrene infection, frequently the plasma CO_2 was well below this figure, and the lowered alkalinity may play a part in producing the critical clinical symptoms. Acidosis then, in early cases of uncomplicated shock, would seem to play a minor and secondary rôle to the generally impaired circulation.

Routine determinations of the red blood corpuscle and haemoglobin content of a unit volume of blood have been repeatedly carried out in shock cases by many observers. The results are somewhat anomalous, for not infrequently in a patient who had undoubtedly lost a considerable amount of blood the red blood corpuscle and haemoglobin estimations closely approximated the normal. Also in cases of extremely severe primary haemorrhage the reduction in corpuscles and haemoglobin percentage was strikingly small in view of the actual amount of blood lost. It therefore appears that the red blood corpuscle content of a unit volume of blood is of less importance in wound shock than is the total amount of circulating blood.

In order to obtain this information, total blood and plasma volume were determined in this series of thirty cases at the

same time as the red corpuscle count, haematocrit reading, and haemoglobin percentage. These estimations were always made on venous blood. The blood and plasma volume methods employed were those devised by Keith, Rowntree, and Geraghty (2). The details of the methods are given in the authors' original paper, and in the communication of Robertson and Bock to the Shock Committee (3). Each patient was weighed before his blood volume was determined and the values obtained compared with that of normal men of the same weight.

Total blood and plasma volumes were found to be consistently reduced, thus explaining the anaemic condition of the patients in spite of a relatively high blood count. Further, it was soon recognized that the diminished blood volume bore a definite relationship to the severity of the patient's clinical condition. In cases with distinct symptoms of shock the blood volume ranged from 51–85 per cent. of the normal, while there was a corresponding reduction of the plasma. The total plasma volume in the same series of cases amounted to from 62–90 per cent. The next step was to ascertain if possible whether the deficiency of blood in the circulation was entirely due to blood lost from the wound, or if other factors played a part in causing the low blood mass. For in normal individuals, such as donors for transfusion, the withdrawal of a considerable quantity of blood up to 800 c.c. is followed by a very rapid return of the blood to its original volume. My studies indicate that not only can the original volume be reached within an hour, but that this compensatory dilution may be carried still further and result in an actual increase in the blood volume. But when the loss of blood is excessive, or when there is a severe trauma, a shock-like condition follows, which is distinguished by a failure of the normal process of spontaneous dilution. Even without haemorrhage shock may be accompanied by a fall of blood volume. This fact was well brought out in a soldier suffering from very severe symptoms of wound shock, who later died. In this case some twenty-four hours after 600 c.c. of gum acacia solution had been injected intravenously, the haemoglobin amounted to 125 per cent. At autopsy no definite external wounds were found except a few superficial bruises, and no gross internal haemorrhage had occurred. In this case the blood volume was not directly determined, but the high haemoglobin percentage, particularly after the injection of the gum solution, indicated a reduction of blood volume of at least 25 per cent. From this striking case one is forced to the conclusion that there are other factors in the production of the low blood volume observed in wound shock than the actual amount of blood lost. However, in the majority of the present series of cases the primary haemorrhage was sufficient to account for the subsequent reduced blood volume.

3. Clinical Types of Wound Shock.

When a convoy of wounded reaches the Casualty Clearing Station a quick and accurate clinical appreciation of wound shock is of great value. The early recognition of the condition permits

of appropriate treatment being immediately instituted, and affords a basis for subsequent observation during the further course of the case. As one's experience with the individual cases gradually increased, distinct clinical types of reaction to shock became evident. Further study soon established a more or less definite relationship between certain symptoms and the extent of blood volume reduction. On the basis then of clinical observation and degree of blood volume reduction, cases of shock were found to fall into three types or groups. For descriptive purposes the groups have been termed: (i) Compensated, (ii) Partially Compensated, (iii) Uncompensated.

Group I. Compensated Cases. In this type of case the patient's general condition is good. He has no distressing symptoms except the local pain of the wound and a feeling of general weakness. He is often very pale, and moderate bleeding may have occurred after receiving the wound. The pulse is increased to 90 or 110, the systolic blood-pressure remains above 100 mm. Hg., and the blood volume is never reduced below 80 per cent. This amount of reduction in blood volume would seem to be the maximum decrease that occurred in this series without giving rise to marked untoward symptoms. The plasma volume does not show a proportionate reduction, being 85 to 90 per cent. of normal, thus giving evidence that dilution though delayed is taking place spontaneously.

Group II. Partially Compensated Cases. Here the patient's general condition is not good. There is usually a history of a smart haemorrhage. He is very pale, restless, thirsty, and vomits readily. The extremities are cold and partially anaesthetic to painful stimuli. The pulse-rate is rapid, 120–140, and difficult to count; the systolic blood-pressure is, as a rule, below 90, usually 70–80 mm. Hg. The blood volume ranges between 65–75 per cent., and dilution has occurred slowly, the plasma volume being 70–80 per cent.

Group III. Uncompensated Cases. These patients are in an extremely serious condition. They are as a rule restless, very thirsty, and vomit immediately on being given fluids, and the extremities are very cold to the touch. The pulse cannot be felt, the blood-pressure having fallen to below 60 mm. Hg. On auscultation the heart-rate is found to be 120 to 160. Certain of these cases have a heart-rate below 100, but this is almost invariably a terminal phenomenon. The blood volume is below 65 per cent. of the normal, frequently between 50 and 60 per cent. The lowest plasma volume obtained was 62 per cent., so that dilution was remarkably retarded.

4. Therapeutic Considerations.

Recovery from shock is associated with a rise in blood volume. In slight cases spontaneous dilution takes place, though retarded. The application of heat, the liberal administration of fluid are generally sufficient to restore the patient's condition to one permitting operation. But in many cases of severe wounds these measures are insufficient to resuscitate the patient. More direct methods for increasing the blood volume are indicated. Normal or even hypertonic saline given intravenously has but a transitory

effect. The addition of alkalis to the saline solution has given no better results in uncomplicated wound shock. Transfusion of whole blood is vastly superior to these solutions in that its effect is more lasting, which was attributed to the replacement of the blood lost. Technical and practical difficulties render this means unsuitable for extended use.

As a substitute for whole blood Bayliss (4) introduced 6 per cent. gum acacia solution, which has the same viscosity as whole blood and the same osmotic pressure as plasma, and found that it gave parallel results in the treatment of experimental shock. Drummond and Taylor (5) tested these results clinically on cases of wound shock, and gave a favourable report. With more general use, however, failures have not been infrequent. In some cases the gum solution itself has been faulty; if it is made up correctly as described by Bayliss, I have found no untoward symptoms follow its use. Sometimes the administration has been at fault; the solution should be warmed to body temperature and run in slowly. But in spite of these precautions, there still remain a certain number of failures. In some of these latter cases I have found that neither the injection of gum nor yet the transfusion of blood has been successful. What experimental data were there at hand to offer an adequate explanation of the success or failure of the gum or whole blood? The fact that 6 per cent. gum acacia is chemically an indifferent fluid, having the same osmotic pressure as blood plasma, suggested the possibility that improvement following its use was due to an increase in plasma and blood volume. An actual increase in plasma and total blood bulk was demonstrated after gum infusion in three cases (Table I) with an initial blood volume of 51 to 60 per cent., and satisfactory recoveries resulted.

TABLE I

Name.	Date.	Medication.	B.P. systol. mm. Hg.	Blood vol. c.c.	Blood vol. % of normal.	Plasma vol. c.c.	Plasma vol. % of normal.
Pte. A. E. K.	20/vi		75	2680	54	1820	62
	20/vi	1000 c.c. 6 % gum acacia (2 injections) operation					
	21/vi		110	2950	67	2300	88
	25/vi		110	3930	91	3180	121
Pte. W. H. P.	12/vii		75	3125	60	2000	65
	12/vii	700 c.c. 6 % gum acacia 1 injection, operation					
	12/vii (12 hrs. later)		90	3380	70	2400	84
	15/vii		115	3570	78	3000	111
	19/vii		120	3840	89	3190	125
Pte. W. E.	10/viii		55	2665	51	2000	66
	10/viii	1200 c.c. 6% gum acacia (2 injections) operation					
	11/viii		115	3230	70	2725	100
	12/viii		120	3620	84	3115	122
	16/vii		120	3310	81	2910	121

As was to be expected, the immediate rise in plasma content was more marked than the increase in total blood-volume. On the other hand, when the gum solution failed to improve the impoverished circulation, failure would seem to be due to the inability of the vascular system to retain the added fluid. Direct blood-volume estimations were difficult to carry out in these cases which failed to respond to the infusion, chiefly because of the low blood-pressure, but in a single instance, Sgt. J. B., Table II, one hour after 1000 c.c. of gum solution had been injected, the increase in total blood-volume was only 200 c.c., and in plasma-volume 420 c.c.

TABLE II

Name.	Time after recg. wound (hours).	Medication.	B.P. systol. in mm. Hg.	Blood vol. c.c.	Blood vol. % of normal.	Plasma volume.	Plasma volume % of normal.
Sgt. J. B.	9		55	3000	58	2030	68
	10½	1000 c.c. 6 % gum acacia					
	11½		?	3180	61	2450	81
	11¾	Patient died					
Pte. A. H.	7½		75	2540	55	1700	63
	10½	Transfusion, 900 c.c. whole blood					
	12		120	2690	58	1830	68
	12¼	Operation					
	12¾	Patient died					

At autopsy, also, in one of these cases that failed to react to the infusion of 1000 c.c., the lungs and subcutaneous tissues were found to be markedly oedematous. These observations, together with the absence of any physiological improvement in the circulation in numerous other cases following gum infusion, led one to the conclusion that the capacity of the blood vascular system to retain or absorb fluid had been permanently damaged. A like explanation for the failure of blood transfusion in cases of wound shock appears to hold good. In one case, Pte. A. H., Table II, with a shattered lower leg and a blood-volume of 55 per cent. of normal on admission, 900 c.c. of whole blood was transfused. Ninety minutes later, no external bleeding having occurred in the interval, actual estimation revealed only the small increase of 150 c.c. in blood-volume. Shortly afterwards the patient died during operation. In a second case in which the blood-volume was not estimated there had been an obviously severe primary haemorrhage, and the systolic blood-pressure was 40 mm. Hg. This patient was transfused with 900 c.c. of whole blood, and a few hours later died in a similar manner on the operating table. At autopsy in both cases there was oedema of the lungs and the tissues generally were more moist than normal, though not actually oedematous. These cases, along with other available data, go to show that failure to increase the fluid in the vascular system following intravenous injection of gum solution or whole blood occurs only when the blood-volume is greatly reduced and the marked reduction has persisted for a certain period of time.

Robertson and Bock (3) have lately demonstrated that after severe haemorrhage—particularly secondary haemorrhage—the ingestion of large quantities of fluid by mouth and per rectum will cause a marked increase in blood-volume. This fact has an important bearing on the treatment of shock cases, more especially when the blood volume is below the critical level. Saline can be forced per rectum, but the administration of fluids by mouth is impracticable in the severe case of shock, because vomiting so readily occurs. The subcutaneous route for the injection of saline would also seem to be contraindicated because of the sluggish peripheral circulation and consequent slow absorption. The urgent immediate need of vascular fluid in serious wound shock must necessarily make the alimentary ingestion of fluid a secondary therapeutic measure to intravenous injection.

5. Plan of Treatment.

Having pointed out the importance of diminished blood-volume in wound shock and discussed the methods already employed to remedy the deficiency, it does not seem out of place to suggest a more detailed plan for the treatment of shock cases. The methods advocated can be carried out with a minimum of special apparatus and offer some very satisfactory therapeutic results. The grouping of cases into three types as outlined previously makes it possible in a very short time to appreciate the proper mode of attack for the individual case. When the shock condition is compensated as in Group I, rest in a warm bed until the surgeon can operate is usually all the care necessary. If symptoms of failing compensation develop during or after operation, fluid can be given, (i) in the form of gum solution intravenously, 500 c.c. as a rule suffices; (ii) saline per rectum by the continuous drip method, or injections of 400 c.c. every two hours. Improvement as indicated by the slowing of the pulse and rise in blood-pressure generally occurs quickly.

The management of the partially compensated cases of Group II is more difficult. The application of heat should first be given a trial. If after one or two hours the pulse does not improve or the blood-pressure rise, the question of increasing the fluid intake must be considered. Fluid by mouth, except in small quantities as a mouth-wash, is contraindicated, for the ingestion of larger amounts soon leads to renewed vomiting. Saline per rectum can be given as a routine measure on admission to the resuscitation ward, and continued periodically for the first twenty-four hours; but in order to obtain a more immediate response, when the trial of heat has failed, an infusion of 500 c.c. of gum solution is indicated. Before administering the infusion a haemoglobin estimation is of value as a basis or starting-point for further determinations. The behaviour of the pulse and blood-pressure is recorded at half-hourly periods following the infusion. If definite improvement persists for two or three hours, surgical treatment can be instituted. However, if the improvement is only transient, a second infusion of gum can be

administered, and frequently then a steady improvement follows, so that an operation can be performed; on the other hand, certain cases fail to respond to a second injection of gum, and if the haemoglobin percentage is low, whole blood transfusion should be given a trial. The anaesthesia of choice for serious shock cases is undoubtedly nitrous oxide and oxygen. Should symptoms of collapse develop during operation more gum can be administered if the patient has not already received a second injection. However, if a second infusion has already been given, blood transfusion is indicated. It is chiefly in the uncompensated cases of Group III that infusions of gum solution and even transfusion of whole blood are of no avail.

Repeated haemoglobin estimations in such cases are of special prognostic value. When dilution is taking place satisfactorily, the haemoglobin percentage gradually falls, but, on the other hand, when fluid is not being retained in the vasular system, the percentage of haemoglobin has little tendency to decrease, and may even show a rise. This latter finding makes the prognosis extremely serious. After dilution has taken place—usually two to six days—and the haemoglobin percentage has dropped to say 30 or 40 per cent., the question of blood transfusion may become very important. This is especially pertinent in cases that are admitted in a state of shock and develop septic complications in the next few days. Further operations may be necessary, and because of the low haemoglobin the possible recurrence of shock becomes a serious problem. Bazett (6) has pointed out in this type of case that a haemoglobin percentage below 35 is near the critical level, and advises the surgeon to be ready to perform a transfusion during the secondary operation. Then again symptoms of shock may also arise after a secondary operation with little or no anaemia present. In one such case the infusion of 500 c.c. of gum solution produced a most satisfactory result. A rib resection was necessary for the proper drainage of a septic chest. Several hours after operation the patient went suddenly into a condition of circulatory collapse, which was indicated by a pulse of 160 and a systolic blood-pressure of 60 mm. Hg. Within an hour of the administration of the gum solution his condition was markedly better, and continued to improve during his further stay of two weeks in the C.C.S. This case affords a striking example of the value of repeated haemoglobin estimations. In less than twenty-four hours from the time of the gum infusion the haemoglobin had fallen from 106 to 80 per cent. That this fall was due to an actual dilution of the blood was indicated by a definite increase in plasma volume.

6. Summary.

1. Reduction of blood volume is a striking and important feature in wound shock.

2. The actual volume of circulating blood must be considered when interpreting the red blood corpuscle count and the haemoglobin percentage.

3. In shock without haemorrhage there is a reduction in blood

volume, but not to such a degree as when haemorrhage has also occurred. With a blood volume below 80 per cent. the patient shows serious symptoms of shock; but below 65 per cent. his condition is critical.

4. In moderate haemorrhage without shock the blood volume is rapidly restored.

5. Cases of wound shock can be divided into three clinical types: (i) compensated; (ii) partially compensated; (iii) uncompensated.

6. Recovery from wound shock is associated with an increase in blood-volume.

7. In some cases of severe wound shock the blood-vessels are incapable of retaining an adequate amount of fluid in the circulation.

8. In severe shock intravenous therapy is essential.

9. An important factor in the treatment of wound shock is to increase the amount of fluid in the circulation. For this purpose 6 per cent. gum acacia solution is very often efficient. When gum solution fails, whole blood should be given.

The author wishes to express his appreciation to Major-General Cuthbert Wallace, C.B., C.M.G., for his constant interest and valuable advice. The author is also deeply indebted to Major A. Tudor Edwards, R.A.M.C., and to Captain Harold Walker, R.A.M.C., for their hearty co-operation in selecting cases and in carrying out the necessary surgical treatment.

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IX. BRIEF SUMMARY OF CHANGES IN THE CENTRAL NERVOUS SYSTEM OCCURRING IN VARIOUS FORMS OF SHOCK

By F. W. Mott, M.D., LL.D., F.R.C.P., F.R.S., Brevet Lieutenant-Colonel, R.A.M.C., T.

A detailed account with illustrations will be published later, but certain conclusions appear to be permissible from examination of the material so far studied histologically by me; at any rate they will serve as an indication for further experiments on animals and for clinico-anatomical investigations.

1. Material Employed.

1. Brains of fatal cases of shell shock, with and without burial, and probable gas-poisoning.

2. Brains of three cases of fatal wound shock

3. Brain of shock from extensive burns.
4. Brains of anaphylactic shock.
5. Brain of fatal shock from contusion of heart.
6. Three brains of animals injected with histamine.
7. A brain from death under anaesthetic prior to injection of antitetanic serum. (This brain was particularly useful, as it showed practically normal nerve-cells.)

All the materials were fixed and hardened in formol saline solution. All were blocked in paraffin, and the sections cut of the same thickness. The staining of the sections was in all cases similar, and the stains used were: (1) Van Gieson, (2) Thionin (Nissl method), (3) Giemsa or Leishman, both of which contain a basophil and an acidophil dye.

Portions of the brains of shock from gun-shot wounds with compound comminuted fractures were cut by freezing, stained with Scharlach, and mounted in glycerine to demonstrate fat embolism. As far as possible all the conditions were similar—this is essential for any comparative study of such fine changes as can be demonstrated by our present technique. The several Silver methods of staining the neuron were tried, but the results are not sufficiently satisfactory to draw any conclusions therefrom.

In a case of shell shock from which there was no possibility of gas-poisoning there were no visible punctate haemorrhages in the white matter. It may be concluded, therefore, that they only occur when there is hyaline thrombosis of the terminal arterioles of the white matter of the brain.

Further consideration of these cases of shock complicated by gas-poisoning will not, therefore, be discussed here.

2. Vascular Changes.

In the definite case of shell-shock and sudden collapse there was obvious right-heart and venous congestion, subpial haemorrhages, multiple minute haemorrhages in various situations, including the medulla and pons, with chromatolytic changes in the nerve-cells.

Before, however, proceeding further we will take the general condition of the vessels in all forms of shock. It may be stated that the clinical notes indicate a great fall of blood-pressure, associated with venous congestion; consequently the vessels of the brain show engorged veins with stasis; more or less subpial haemorrhages; sometimes haemorrhage into the peri-adventitial sheaths; dilatation of the perivascular and perineuronal spaces of varying degree, but more marked than can be accounted for by shrinkage caused by the hardening fluid. Collapsed empty arterioles, capillaries, and venules are seen in the dilated spaces, and that the spaces are not artifacts is probable from the fact that minute trabeculae can be seen stretching across the space to the surrounding tissue. Moreover, this condition accords with the observation made post-mortem that the brains were wetter than usual. Again, I have found that the changes correspond closely with the appearances presented by the brains of animals in which the vertebrals and both carotid arteries have been tied.

There seems, then, to be definite evidence pointing to a cerebral anaemia. In some brains there were, besides the collapsed capillaries, marked appearances of scattered areas of capillary stasis and engorged veins.

In two of the cases of gun-shot wound with comminuted fracture there was definite evidence of fat embolism in the medulla and the cortex; it is probable that the same condition would have been found throughout the brain by searching. I did not think, however, that fat embolism was of itself the sole cause, or even the most important cause, of the changes found in the cells, although it may have been an important associated factor.

3. Cell Changes.

The changes in the cells may be divided into two classes: (1) The change in the amount of Nissl substance and the integrity of the Nissl bodies; (2) the change in the colour reactions. The former may be regarded as evidence of exhaustion of the Nissl substance, the latter as evidence of a bio-chemical change in the cytoplasm.

4. Chromatolytic Changes of the Nerve-cells.

Comparative examination was made of sections, particularly of the medulla and of the cerebellum, which two regions were chosen because the former contains the vital centres and the latter because of its uniform structure.

A broad statement may be made that a comparison between the appearances of the cells of these structures in all the cases of fatal shock with a continued fall of blood-pressure, and the sections of the brain from the case of sudden death under an anaesthetic, showed a more or less considerable difference in the amount of basophil substance and integrity of the Nissl bodies.

In the cases of shock, where for some hours prior to death the patient suffered with a very low blood-pressure, there is quite an obvious difference in this respect; in fact there is a general chromatolysis, which we therefore may associate with prolonged anoxaemia.

Comparative photo-micrographs of the dorsal nucleus and ventral nucleus of the vagus of the normal and shock cases show a marked difference in the amount of basophil substance; likewise the cells of Purkinje of the cerebellum.

5. Bio-Chemical Changes of the Cytoplasm.

The second change in colour reaction, which we know occurs in hyperpyrexia and toxic conditions of the blood, is an alteration in the staining reaction. The Nissl stain is not a bright blue, and when a double stain such as a basic blue and eosin dye is used the cells stain a dull purple. The cytoplasm is more diffusely stained, and the Nissl bodies are not so evident. All the cells are more or less thus stained, though in varying degrees of intensity. This denotes a bio-chemical change in the cell. It occurs when the

blood-supply is completely cut off, because the cell dies. This change in the colour reaction, therefore, denotes a death change. Now, in one of the brains of the animals which were injected with histamine, sent to me by Dr. Dale, the experiment was so arranged that immediate shock was prevented by slow injection, and in this brain I found a most pronounced bio-chemical change in the colour reaction, of many of the cells as compared with two other brains in which immediate shock was produced, and a fall of blood-pressure induced.

In the light of this observation I re-examined the sections of the brains of cases of traumatic shock, and I found that many of the cells of the medulla and some of the Purkinje cells showed a tendency to a diffuse purple staining, or the cytoplasm stained with the acidophil dye. The cases which appeared to me to show this altered colour reaction were cases of shock with extensive laceration of tissues and the case of burn shock. Especially was the cell reaction noticeable when similar groups of cells were compared with those from the case of death under an anaesthetic. Having regard, however, to the difficulties besetting a comparison based on colour reaction, too much importance must not be attached to these observations.

Should similar results be obtained by further investigation of the brains of patients dying from shock, and of the brains of animals in which the condition has been produced experimentally, they would lend support to the view that toxins, by their effect on the nervous system, play an important part in the production of shock.

It is unlikely that the changes produced by shock in the cells of the central nervous system are all due to one cause. Several factors may be concerned.

(1) The cerebral anaemia caused by fall of blood-pressure, whether due to haemorrhage, vasomotor failure, or capillary stasis, would account for some of the changes that can be detected.

(2) Fat embolism may play a part in some cases.

(2) Prolonged pain and stress may cause a general devitalization of the nervous system.

(4) Toxic substances from damaged tissues may directly affect the nerve-cells.

If confirmation of this last named effect is obtained, the bio-chemical change in the nerve-cells, so produced, may prove to be the most important factor in causing a fatal termination; for when it had once occurred in the vital centres, remedial measures such as transfusion of blood, injection of gum-solution, warmth, and stimulants would be of little value.

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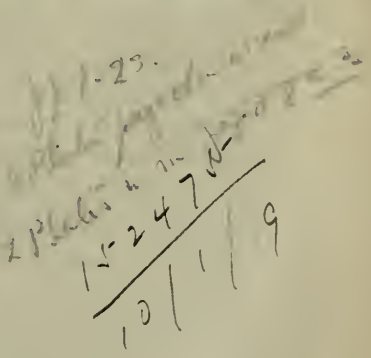

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BLOOD VOLUME CHANGES IN WOUND SHOCK AND PRIMARY HÆMORRHAGE

Captain N. M. Keith, R.A.M.C.

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I. Introduction.

The fundamental cause of wound shock still remains obscure. No single etiological factor has been suggested as the invariable cause. That there are many secondary contributory factors seems clear; but when these are largely eliminated by early preventive measures, the condition often persists and the patient succumbs. In view of this lack of knowledge as to the initial cause and subsequent development of shock, it must be recognized that the condition met with clinically is the end result of a primary and several contributory causes. Clinical observation and physiological studies all go to show that shock, when fully developed, is essentially a partial suspension of the circulation. This state of defective or altered circulation will account for practically all the phenomena commonly seen in wound shock such as pallor, thirst, rapid pulse, low blood pressure, and capillary stasis. Most of these symptoms are similar to those seen in severe anæmia. But in shock the blood picture when determined by the usual methods, unit volume estimations of the red blood corpuscles and hæmoglobin percentage, does not indicate the degree of anæmia one would expect to find with the accompanying symptoms. This apparently anomalous condition may be explained if the total volume of blood in the circulation is considered in relation to its several components. From this point of view it was thought that blood volume determinations might show that the total amount of

blood in the circulation is definitely reduced, and that this reduction would account for the clinical picture as seen in shock. The chief object of the present investigation was to make blood volume determinations in cases presenting clinical symptoms of wound shock, and ascertain whether changes in blood volume bore any definite relationship to the severity of the condition.

II. Methods of Study.

1. *Blood and Plasma Volume.*

Methods for determining the total amount of blood in the circulation have been the subject of much thought and study on the part of physiologists. Welcker (1), as far back as 1854, washed out completely the blood vascular system of animals, and from the amount of hæmoglobin recovered estimated the total blood volume. Since Welcker's time this has been the standard experimental method, though many workers have improved the actual technique employed. With the object of devising a method that would be applicable during life and have no injurious effect upon the animal, the idea of injecting a non-toxic, non-diffusable dye substance into the blood stream and estimating its dilution was suggested. Keith, Rowntree, and Geraghty (2) were able to show that the dye vital red (a chemical compound belonging to the triphenyl-methane series) fulfilled in large measure these conditions. It was proved that the dye did not pass into the red blood corpuscles to any appreciable extent, so that dilution was taking place in the plasma only. Knowing, then, that the dye dilution simply gave an estimation of the total circulating plasma, it was necessary to make a further determination of the relative volumes of red blood corpuscles and plasma in order to determine the total blood volume. This can be readily done with the hæmatocrit. Vital red was found to be non-toxic in man at the dose necessary to give satisfactory colour readings, and for the results in normal men and in certain pathological conditions the reader is referred to the original paper (2). The value of estimating plasma volume as distinct from the total blood mass will be well brought out in the results obtained in the present work. The absolute values obtained for the total blood in normal men by this method vary from 1/13 to 1/10·5 of the body weight. These figures are slightly higher than that obtained by Bischoff (3), who washed out the blood of beheaded criminals immediately after death and found the blood volume to average 1/13 of the body weight. That the absolute figures obtained by the vital red method may be slightly higher than the actual amount of blood present seems probable on theoretical grounds. We know from experiments that during the first ten minutes after injection, the amount of vital red in the circulation remains at practically the same level. Comparative experiments in animals with the vital red method and by washing out the total hæmoglobin should afford evidence as to whether an immediate initial loss of the dye occurs. However, for relative values the vital red method gives very accurate results.

The chief details of the method are as follows. The dye is made up

as 1·5 per cent. solution in *freshly distilled* water, and placed in small flasks in quantities sufficient for one test, 15–20 c.c. The solution is then sterilized by boiling for five minutes or by placing in an autoclave at 1–2 pounds pressure for 20 minutes. A certain amount of evaporation of the solution takes place, but as a sample of the injected solution is used in making up the control standard no inaccuracy results. The dose is 3 mg. per kilo of body weight. It is not necessary to grade the dose to less than 1 c.c. as the important point is to know the exact amount injected. From 10–18 c.c. are the amounts usually given, depending upon the size of the individual. Paraffined tubes are used for collecting the specimens of blood, and clotting prevented by the use of a small quantity of finely powdered potassium oxalate in the withdrawal syringes. To prevent hæmolysis, absolutely dry syringes must be used for the withdrawal of the blood. In performing the test one first removes 6–8 c.c. of blood from an elbow vein, and the syringe is disconnected from the needle, which is left in the vein; the syringe containing the known quantity of vital red solution is connected immediately with the needle in the vein, and the dye slowly injected. The first blood sample is gently shaken up in the withdrawal syringe and poured into a paraffined tube. Three to five minutes after the injection the second specimen of blood, 8–10 c.c., is withdrawn into a third syringe and after mixing emptied into two paraffined tubes. From one of these second samples blood can be drawn up into the hæmatocrit tube. The hæmatocrit and the paraffined tubes (tightly corked) are then centrifuged at a high speed for 20 minutes and the plasma pipetted off. In order to read the test a dilute standard dye solution is made up by diluting 0·5 c.c. of the original dye solution to 100 c.c. with 0·8 per cent. of NaCl solution. The two solutions for comparison are made up as follows:

Standard { 1 part of the diluted dye solution;
1 part of the plasma before dye injection;
2 parts 0·8 per cent. NaCl solution.

Test { 1 part of plasma after dye injection;
3 parts 0·8 per cent. NaCl solution.

1 c.c. was taken for convenience as 1 part. The two solutions are then compared in a Duboscq colorimeter and the test or unknown solution read off in percentage against the standard.

The following formula is used for calculating the plasma volume:

$$\frac{200}{R} \times \text{No. of c.c. dye injected} \times 100 = \text{c.c. plasma.}$$

R = per cent. reading of test solution.

The blood volume is calculated from the hæmatocrit reading

$$100 : \text{per cent. plasma} :: x : \text{c.c. plasma.}$$

Hæmolysis must be avoided, for when it takes place a brownish tint is given to the test solution of plasma, which makes the colorimeter reading difficult.

In the present series of cases each patient was weighed before the test was made, and the values for total blood and plasma were compared with those of normal men of the same weight. These values are expressed as percentages in the charts accompanying this

paper. Normal blood and plasma volumes were found in man to average 35 and 50 c.c. per kilo of body weight.

2. *Hæmoglobin Estimation.*

The method used was that described by Palmer (4). Briefly it consists in comparing in the colorimeter a 1 per cent. carbon monoxide solution of the test blood with a standard solution of 1 per cent. carbon monoxide hæmoglobin. The standard solution is made up by mixing an equal amount of blood from a number of normal individuals and diluting the total amount of blood so as to make a 1 per cent. solution of hæmolysed blood in a 0·4 per cent. ammonia solution. Coal gas or carbon monoxide is then bubbled through till all the oxyhæmoglobin is changed into carbon monoxide hæmoglobin. This standard will keep its colour for several months. The oxygen carrying capacity of the standard solution was not determined, as the necessary apparatus for carrying out the estimation was not available. To perform the test 0·2 c.c. of blood was accurately measured into a small pipette and then delivered into a 20 c.c. volumetric flask containing several c.c. of 0·4 per cent. ammonia solution. The pipette is washed several times with the solution in the flask. The flask is next filled up to the mark with ammonia solution and well shaken. The contents are then poured into a large test-tube and coal gas or carbon monoxide is bubbled through the solution for about 30 seconds, this period of time ensuring thorough saturation. The colour of this unknown test solution is compared with the standard hæmoglobin solution in a Duboscq colorimeter, and its percentage determined. Hæmoglobin estimations were only made with venous blood in this study. For general clinical work in shock, when extremely accurate readings are not necessary, the Haldane-Gowers hæmoglobinometer is quite satisfactory.

3. *Other Methods.*

The small hæmatocrit tubes were used for the hæmatocrit reading. The red blood corpuscle count was made in usual manner, using Hayem's solution as the diluent.[1] The blood for the white blood corpuscle count was diluted with 1 per cent. acetic acid. Blood pressure was estimated by the auscultatory method, using the Tycos spring sphygmomanometer. When the pulse, as felt at the wrist, was very rapid and feeble, the heart rate was determined directly by means of the stethoscope.

III. The Relation of Blood Volume to Wound Shock.

Total blood and plasma volumes were found to be consistently reduced in soldiers suffering from wound shock. Further, the diminished blood volume was soon recognized to bear a definite

[1] Comparative results in the estimation of the red blood corpuscle content of blood went to show that the hæmatocrit reading was much more accurate than actual enumeration of the cells in the counting chamber. When determined by the method outlined above, relative changes in the hæmoglobin percentage could be estimated with great accuracy. A hæmatocrit reading of 42 per cent. volume of red blood corpuscles has been considered as the average normal figure. In the accompanying charts the hæmatocrit readings have been expressed as percentages, taking 42 as 100 per cent.

relationship to the severity of the patient's clinical condition. 29 cases with definite symptoms of wound shock form the basis of the present study. In 27 of these the estimated blood volume ranged from 52 to 85 per cent. of the normal, while there was a corresponding reduction in the plasma to from 62 to 90 per cent. In the remaining two cases the hæmoglobin percentage and clinical symptoms indicated a marked reduction in blood volume, although this was not directly determined.

The next step was to ascertain if possible whether the deficiency of blood in the circulation was entirely due to blood lost from the wound, or if other factors played a part in causing the low blood mass. For in normal individuals, such as a donor for transfusion, the withdrawal of a considerable quantity of blood up to 800 c.c. is followed by a very rapid return of the blood to its original level, e.g. G, in Table I. Dreyer and Walker (5) have made the same observation on experimental animals. The reaction in this donor would indicate that not only can the original volume be reached within an hour, but that the compensatory process of supplying fluid to the circulation may be carried still further and result in an actual increase in the blood volume. However, when the loss of blood is excessive or when there is severe trauma, a shock-like condition follows which is distinguished by a failure of the normal process of rapid restoration of fluid to the vascular system. Even without hæmorrhage shock may be accompanied by a fall of blood volume. This fact was well brought out in a soldier suffering from very severe symptoms of wound shock, who later died (S. S., Table IV). In this case, some 24 hours after 600 c.c. of 6 per cent. gum acacia solution had been injected intravenously, the hæmoglobin amounted to 125 per cent. At autopsy no definite external wounds were found except a few superficial bruises, and no gross internal hæmorrhage had occurred. The blood volume was not directly determined in this case, but the high hæmoglobin percentage, particularly after the injection of the gum solution, indicated a reduction of blood volume of at least 25 per cent. From this striking case one is forced to the conclusion that there are other factors in the production of the low blood volume observed in wound shock than the actual amount of blood shed. However, in a considerable number of the present series of cases the primary hæmorrhage appeared sufficient to account for the subsequent reduced blood volume.

Further study established a more or less definite relationship between certain symptoms and the extent of the blood volume reduction. On the basis, then, of clinical observation and the degree of blood volume reduction, cases of wound shock were found to fall into three classes or groups.

Group I. In this type of case the general condition of the patient is good and he has no distressing symptoms. There is often marked pallor and a record of moderate primary hæmorrhage. The pulse rate is increased to 90–110, the systolic blood pressure remains above 95 mm. Hg., though the pulse pressure may be lowered. The blood volume is never below 75 per cent. of the normal (case R. F., Table II). This amount of reduction in blood volume would seem to be the maximum decrease that occurred in this series without giving

rise to marked persistent untoward symptoms. The plasma volume does not show a proportionate reduction, being 85 to 90 per cent. of the normal, thus giving evidence that the needed fluid is slowly but spontaneously passing into the blood stream.

Group II. Here the patient's general condition is serious. The pulse rate is rapid, 120–140, the systolic blood pressure as a rule below 90, usually 70–80 mm. Hg., and the pulse pressure lowered. The total volume of blood ranges between 65 and 75 per cent., and the plasma volume between 70 and 80 per cent. (case J. A., Table II).

Group III. These patients are dangerously ill. The pulse cannot be felt, the systolic blood pressure having fallen to 60 mm. Hg. or less. On auscultation the heart rate is 120–160. In certain of these cases the heart rate falls below 100, and when this occurs the outcome is almost invariably fatal (case J. A., Table IV). The blood volume is below 65 per cent. of the normal, frequently between 50 and 60 per cent. The lowest plasma volume obtained was 62 per cent., so that the passage of fluid into the vascular system was materially retarded.

IV. The Leucocyte Count in Wound Shock.

Govaerts (6) reports a definite leucocytosis in wound shock. This observation was confirmed in a number of cases in this series. The highest counts were between 30,000 and 39,000, and were always found in cases with wounds of the extremities in which severe primary hæmorrhage had probably occurred. On the other hand the cases with internal wounds involving the viscera, even with an associated primary hæmorrhage, did not show a striking leucocytosis, the highest recorded in this series being 22,000. The decrease in blood volume does not appear to account for the leucocytosis so frequently observed.

V. Blood Volume Changes in Cases with Recovery.

The rapid addition of fluid to the circulation after a moderate hæmorrhage suggested that a similar but modified process possibly occurred in cases recovering from wound shock. Then again, the intimate relationship between diminished blood volume and the characteristic symptoms of wound shock, as seen in this series of cases, also indicated that the actual volume of circulating blood must be increased in order that recovery could occur. With the object of ascertaining the blood and plasma volume changes in such cases the following case was closely observed and blood studies repeated at frequent intervals. The wounded soldier, M. M., Table II, reached the casualty clearing station 12 hours after receiving the wound, which consisted of an extensive comminuted fracture of the left femur. There was no external laceration of the skin and consequently no wound infection. He presented all the characteristic symptoms of wound shock as outlined in cases of Group II. The blood and plasma volumes were respectively only 64 and 69 per cent. of the normal. The pulse rate was 120, the systolic blood pressure 70, and the pulse pressure 20 mm. Hg. Treatment consisted simply in the application of heat and administration of a fluid diet. Next day the patient was clinically much improved,

LEGEND: ✚ Blood Pressure (Systolic and Diastolic)
● Pulse Rate □ Haematocrit
○ Blood Volume △ Plasma Volume

46.27. 8

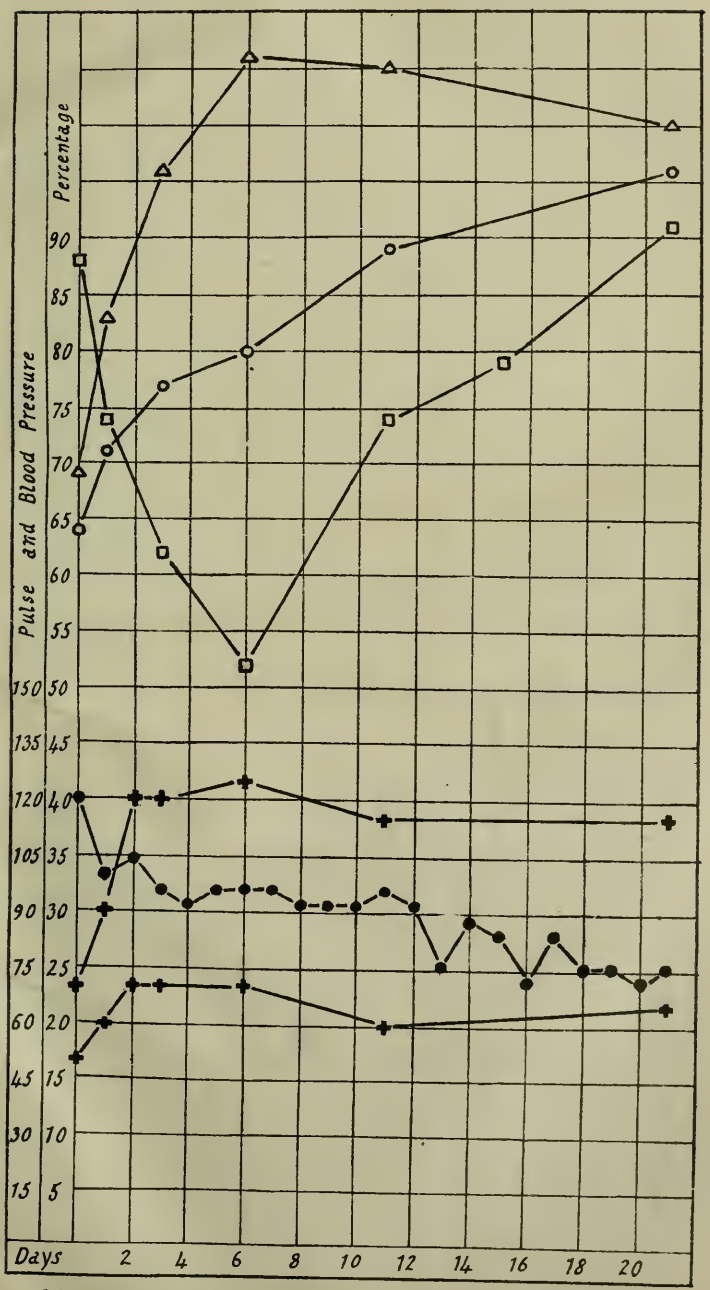

CHART I CASE M.M. TABLE II

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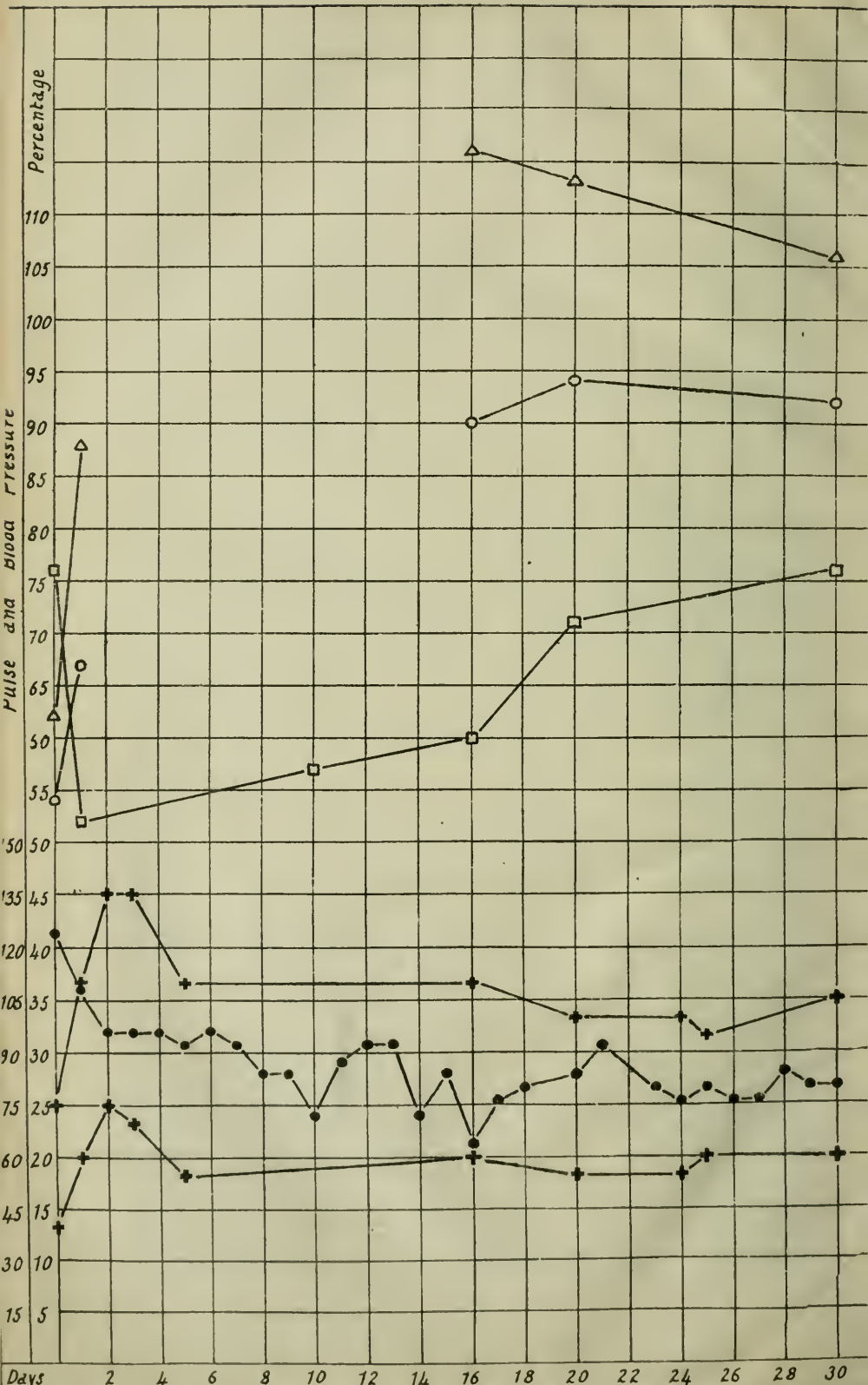

CHART II CASE A.E.K. TABLE III

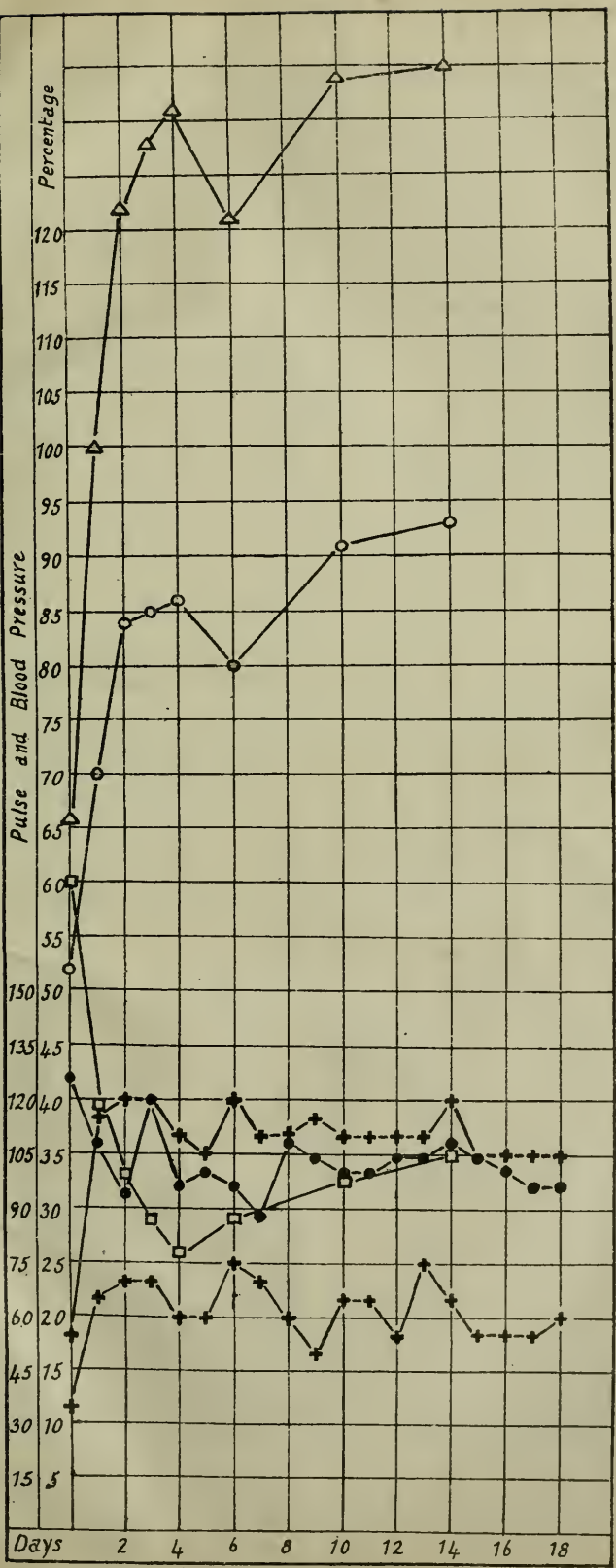

CHART III CASE W.E. TABLE III

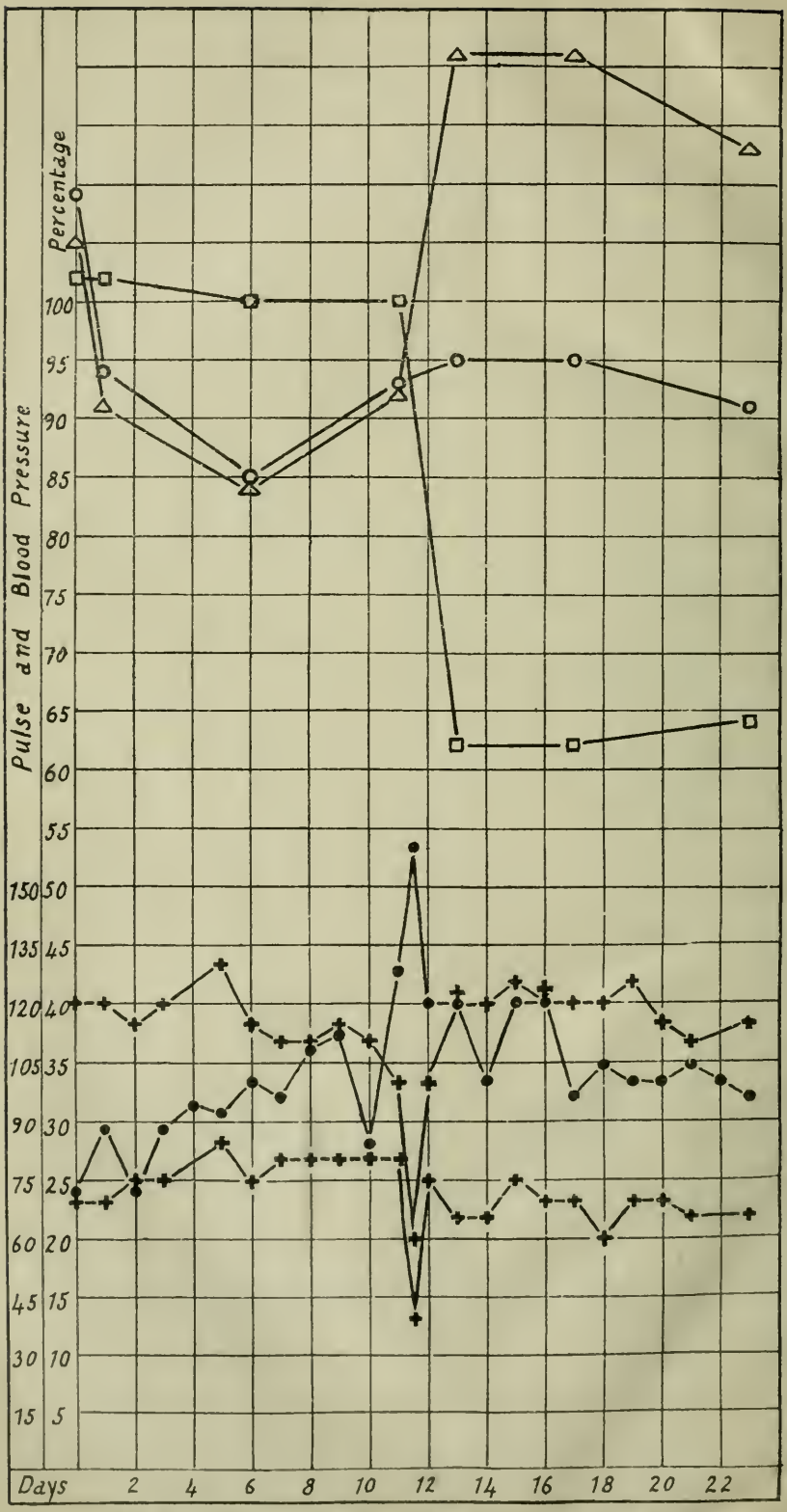

CHART IV CASE J. MoP. TABLE III

3358 36/211 2000 5/13 W G. & S.

as shown by a slower pulse rate and rise in blood pressure. The total blood volume had been increased 400 c.c. and the plasma volume 500 c.c. On subsequent days during the first week his clinical improvement was gradual and definite, and at the same time the blood volume steadily increased. See Chart I. Attention is drawn to the more rapid and greater proportionate increase in plasma volume than in the total blood mass. Associated with this addition of fluid to the circulation, there was a marked decrease in the number of red blood corpuscles, in the hæmatocrit reading, and hæmoglobin percentage. This spontaneous partial restoration of the blood volume by the rapid addition of fluid and consequent dilution of the remaining red blood corpuscles appears to continue until the fourth to sixth day after the primary hæmorrhage and shock. From that time onwards the rise in the number of red cells and hæmoglobin percentage is steady, and the total blood mass increases proportionately. Robertson and Bock (7) noted this fact in patients recovering from secondary hæmorrhage. The early high plasma percentage tends gradually to diminish as the number of red cells increases. Practically normal values were obtained for blood and plasma volumes, red blood corpuscles, hæmatocrit and hæmoglobin content on the twenty-first day after the wound was received. Spontaneous recovery from wound shock as described in the above instance occurred in three further cases, two of which underwent a surgical operation. No intravenous injections were needed to bring about an adequate restoration of blood volume. A second series of six cases presenting serious symptoms of wound shock had an initial blood volume ranging from 52 to 72 per cent. Clinically they belong to Groups II and III. Infusions of 6 per cent. gum acacia or a transfusion of whole blood were administered before or at the time of operation. Recovery was again accompanied by an increase in blood volume due in large part to a rapid addition of fluid to the total plasma. This was especially marked following the infusion of 6 per cent. gum acacia. Charts II and III illustrate the same phenomena as seen in Chart I, but with this difference, that the addition of fluid to the blood stream appears to take place more quickly and to form a larger total amount of the blood mass. This difference may be due to the bulk of gum directly added or to the stimulation of the natural process of blood volume restoration. In these two cases the red blood corpuscle content reached the minimum level at approximately the same period as seen in Chart I, but the later gradual rise in the number of red cells seemed to occur more slowly. This tardy increase in the number of red cells was a marked feature of the case shown in Chart III, though the general condition and clinical progress of the patient was excellent. Here on the eighteenth day after being wounded the hæmatocrit reading and hæmoglobin percentage were only 36 per cent. Case S., Table III, offers a striking contrast to those serious cases in which recovery followed infusion of gum solution only. The patient was given both gum and whole blood[1] intravenously, and though there was initially a marked

[1] When whole blood transfusion was performed in these cases, the Kimpton-Brown paraffin tube was used. The blood of donor and of recipient was always tested for 'compatibility'.

reduction in blood volume and a subsequent large addition of fluid to the blood stream, the minimum hæmoglobin percentage on the fourth day amounted to the relatively high figure of 58 per cent.

The blood and plasma volume changes that occurred in the case McP., Chart IV, were of great interest. Ten hours after this patient was wounded his blood volume was high and, calculated on a basis of the patient's weight, was above the normal. This large volume of blood may have been due to the fact that the individual was of a full-blooded type, as normal controls were found to show as great variations from the general average. However, the facts that the patient had lost at least 300 c.c. of blood when wounded, and twenty-four hours after did show a definite reduction would rather suggest that an early rapid restoration had occurred, as in the donor G. G., Table I. Six days later, although his clinical condition was good, and the pulse and blood pressure satisfactory, a distinct further decrease in blood volume had occurred. Close observation was continued, and on the eleventh day unfavourable symptoms developed, including a rise in temperature and pulse rate. These untoward symptoms were associated with a slight rise both in blood volume and hæmoglobin percentage. Aspiration of the right chest revealed the presence of fluid infected with streptococci. A wide rib resection was carried out under a short nitrous oxide anæsthesia, and 2,200 c.c. of blood-stained infected fluid removed from the right chest. The patient apparently stood the operation well, but during the next eight hours symptoms of circulatory collapse developed. At the end of this time the pulse rate was 160 and barely perceptible, and the systolic blood pressure fell to 60 mm. Hg. The pulse pressure showed a pronounced reduction to 20 mm. of Hg., a finding so frequent in serious conditions of shock. An infusion of 600 c.c. of 6 per cent. gum solution was given immediately. Within an hour his general condition was improved, the pulse rate dropping to 120 and the systolic blood pressure rising 100 mm. Hg. Nine hours later the patient showed a remarkable improvement, his hæmoglobin value standing at 80 per cent. Blood studies made 42 hours after operation showed a further decrease in the hæmoglobin to 62 per cent. Thus a decrease in hæmoglobin from 106 to 62 per cent. had occurred since the time of operation, and with this remarkable fall the patient's condition was markedly improved. During the same period the plasma volume had increased 800 c.c., or on a basis of body weight 28 per cent., although there was only the very small addition of 50 c.c. to the total blood volume. It is quite evident that the actual decrease in red cell and hæmoglobin content in this case during recovery from shock was not simply due to the increase of plasma in the circulation. If such a process had occurred the blood volume would also have increased proportionately. This remarkable rise in total plasma without a corresponding rise in the total amount of blood is striking evidence that hæmoglobin was being rapidly lost from the blood while fluid was steadily passing into and being retained in the circulation.

The early partial restoration of blood volume by a rapid increase in the fluid content of the blood has been repeatedly emphasized above as an important phenomenon associated with recovery from

wound shock. In order to demonstrate that this fluid increase may or may not coincide with a proportionate decrease in the red cell and hæmoglobin content of the blood, the results in the following cases have been tabulated. In case J. A., the increase in plasma of 18 per cent. is roughly proportional to the decrease of 21 per cent. in hæmoglobin, although the hæmatocrit drop is somewhat greater. The addition of fluid to the blood has resulted in a dilution of the colouring matter of the blood much as if the vascular system were a closed vessel containing a known amount of indicator. The results obtained in the other six cases, on the contrary, show a striking disproportion between the increase in fluid and the reduction in hæmoglobin. In the five cases, M. M., F. E. C., R. J., W. H. P., and J. McP., the fall in hæmoglobin is relatively much greater than the rise in

Name.	*Table.*	*Period of time. Days.*	*Increase in blood vol. c.c.*	*Increase in plasma vol. c.c.*	*Increase in plasma vol. in per cent. of initial blood vol.*	*Decrease in hmgl. in per cent. of initial hmgl.*	*Decrease in hæmatocrit in per cent. of initial hæmatocrit.*	*Intravenous medication.*
M. M.	II	6	760	1,185	30	—	41	None
J. A.	II	7	375	620	18	21	27	None
F. E. C.	II	1	90	410	12	25	30	None
R. J.	IV	2	632	945	27	39	41	Gum, sod. bicarb.
W. H. P.	III	7	715	1,190	38	56	52	Gum
J. Mc P.	III	6	50	800	17	40	38	Gum
S.	III	3	1,230	1,350	43	30	36	Gum, whole blood

plasma. The simplest explanation for this loss of hæmoglobin would be that additional blood had been lost between the two determinations. Such loss did take place at the operation on F. E. C., but no striking loss of blood was observed during this intervening period in W. H. P. and R. J. That additional blood could have been lost in the case of M. M. seems improbable, since he had no open wound and the fractured leg was kept at rest in a Thomas splint. These results at least offer some evidence that a certain amount of red cell destruction may occur in the body during the period when fluid is being added quickly to the circulation. The plasma of M. M. did suggest the presence of bile pigment, but unfortunately urobilin was not tested for in the urine. The definite disproportionate decrease in hæmoglobin and red cell content occurred, as will be noted, both in cases that received and did not receive intravenous infusions. On the other hand, case S., who alone was given gum and whole blood, intravenously, showed the usual increase in plasma, but not the corresponding proportionate decrease in red cell content.

VI. Fatal Cases.

It is a depressing but well-recognized fact that the death-rate is high among wound-shock cases reaching the casualty clearing stations. The difficulties in treating the condition effectively are largely due to our meagre knowledge concerning the fundamental cause and to conditions at the front during active fighting. Another

important factor that has constantly to be kept in mind when considering the outcome of wound shock is the rôle played by early wound infection. In the present series of cases sixteen terminated fatally (Table IV). The original condition of shock tended to persist in eight of these, and would seem to be the cause of death. A secondary hæmorrhage following an operation in a ninth case resulted in collapse and immediate death. Causes other than wound shock accounted for the fatal termination in the remaining seven cases. Of these five were the result of wound infection.[1] Two of the latter cases, L. L. and R. J., on admission to the C.C.S. had all the serious symptoms of shock, and following intravenous medication made a remarkable immediate recovery. Clinical improvement was accompanied by a marked rise in blood pressure and increase in blood volume. Thorough surgical treatment was carried out, but both patients died approximately four days after being wounded. There was a definite ascending gas gangrene infection of the left thigh in the case L. L., while R. J. succumbed to a virulent streptococcal septicæmia. Extensive laceration of the brain in the case N. V. C. was sufficient to account for the fatal outcome. A seventh case had a moderate degree of shock on admission, but failed to respond after effective surgical treatment, and died as the result of a secondary pneumonia. At autopsy the trachea showed the typical lesions due to mustard gas poisoning. The eight cases which undoubtedly suffered from wound shock and eventually died from no other demonstrable cause are of great interest, particularly in relation to alterations in blood volume. J. Br. and A. G. received no intravenous treatment. The former had an extremely low blood volume and spontaneous addition of fluid to the circulation failed to occur. Owing to the pressure of work at the time an infusion of gum was not administered. This was keenly regretted as very similar cases noted previously responded well to repeated injections of 6 per cent. gum solution. The case A. G. was remarkable in many respects. On admission there were definite symptoms of shock, but the blood volume reduction was moderate in degree. Following operation there was a temporary improvement, but the blood volume tended slightly to decrease. This fact made the prognosis serious, which was borne out by subsequent events. On the fourth day following the injury the blood volume was still further reduced, and shortly afterwards the patient died. Evidence of a loss or destruction of red blood cells was shown by a relatively greater decrease in total blood than in plasma volume. The finding at autopsy of 600 c.c. of free blood-stained fluid in the peritoneum and a lacerated liver possibly explain the loss of blood volume and also the greater proportionate decrease of red blood corpuscles. It must also be noted that the initial symptoms of shock were associated with a blood volume 84 per cent. of the normal, while with the terminal fall in blood pressure the volume was considerably lower. J. A., with no external injury, had a blood volume of only 55 per cent. Gum infusion failed to produce any physiological response. At autopsy a fractured pelvis and an extra-peritoneal hæmatoma were

[1] Major J. W. McNee, R.A.M.C., No. 3 Mobile Laboratory, kindly carried out the bacteriological examination in these cases.

found. The clot was measured as accurately as possible and found to amount to 1,000 c.c. This was a much smaller blood loss than the actual determination during life would indicate, and it is evident that in shock with hæmorrhage the actual blood lost cannot always account for the markedly reduced blood volume. In the case J. Bt., blood volume determinations were made before and after the intravenous injection of a litre of gum. There was no clinical sign of improvement following the infusion. One hour later, shortly before death, the blood volume had only increased 200 and the plasma volume 400 c.c. Similarly, the case G. W. W. failed to react to the infusion of 1,000 c.c. of 6 per cent. gum. This man was in very good condition some eight hours after receiving the wound, had no symptoms of shock, and little reduction of blood volume. He stood operation well, but a few hours later passed into a state of collapse. That blood concentration had occurred was evident from the fact that the hæmoglobin percentage had risen from 104 on admission to 120 some sixteen hours later. The injection of gum at this period failed to produce any beneficial response, and at autopsy the lungs and subcutaneous tissues were found to be markedly œdematous. Such observations on these two cases, together with the absence of any persistent physiological improvement in the circulation in numerous other cases of wound shock following gum infusion, lead one to the conclusion that the capacity of the blood vascular system to retain fluid had been permanently damaged. A like explanation for the failure of blood transfusion in wound shock appears to hold good. In the case of A. H., with a blood volume 55 per cent. of normal on admission and systolic blood pressure of 75 mm. Hg., 880 c.c. of whole blood was transfused. Two hours later, no external bleeding having occurred in the interval, actual estimation revealed only the small increase of 150 c.c. in blood volume, and yet the systolic and pulse pressures rose to 130 and 45 mm. Hg. Shortly afterwards the patient died during operation. Another case, M. L., in which the blood volume was not estimated, there had been an obvious severe primary hæmorrhage, and the systolic blood pressure was 45 mm. Hg. This patient was transfused with 880 c.c. of whole blood, and a few hours later died in a similar manner to A. H. At autopsy in both these cases there was œdema of the lungs, and the tissues generally were more moist than normal though not actually œdematous. These cases go to show that a failure to increase the blood vascular fluid following intravenous injection of gum solution or whole blood occurs only when the blood volume is greatly reduced and the marked reduction has persisted for a certain period of time.

VII. Therapeutic Considerations.

Recovery from wound shock has been shown to be associated with a rise in blood volume. The application of heat and the liberal administration of fluid are in many cases sufficient to restore the patient's condition to one permitting operation. But, as previously pointed out, there are cases with severe wounds in which these measures fail to resuscitate the patient. More direct methods for increasing the blood volume are indicated. Normal or even

hypertonic saline given intravenously has but a transitory effect. The addition of alkalies to the saline solution has given no better results in uncomplicated wound shock. Transfusion of whole blood is vastly superior to these solutions in that its effects are more lasting. Technical and practical difficulties render this means unsuitable for extended use. As a substitute for whole blood Bayliss (8) introduced 6 per cent. gum acacia solution, which has the same viscosity as whole blood and the same osmotic pressure due to colloids as plasma, and found that it gave parallel results in the treatment of experimental shock. Drummond and Taylor (9) tested these results clinically on cases of wound shock and gave a favourable report. With more general use, however, failures have not been infrequent. In some cases the gum solution itself has been faulty; if made up correctly as described by Bayliss I have found no untoward symptoms follow its use. Sometimes the administration has been at fault; the solution should be warmed to body temperature and run in slowly. But in spite of these precautions there still remain a number of failures (J. Bt., G. W. W., Table IV). In some of these severe cases, such as A. H. and M. L., Table IV, the transfusion of whole blood also failed. With regard to the relative merits of gum and whole blood in the treatment of shock, I have found in this series of cases the results following intravenous injections of these substances were practically identical, and the success or failure of either depended largely upon whether the blood volume was partially restored after their injection. It is probable that there are cases of shock in which the transfusion of whole blood would give better results than gum, but such cases did not come under my observation.

Robertson and Bock (7) have lately demonstrated that after severe hæmorrhage—particularly secondary hæmorrhage—the ingestion of large quantities of fluid by mouth and per rectum will result in a marked increase in blood volume. This fact has an important bearing on the treatment of shock cases, more especially when the blood volume is below the critical level. Saline can be forced per rectum; indeed, four litres were absorbed in twenty-four hours in the case W. E., Table III. But the administration of fluids by mouth is impracticable in the severe cases of shock because vomiting so readily occurs. The subcutaneous route for the injection of saline would seem also to be contra-indicated because of the sluggish peripheral circulation and consequent slow absorption. The urgent immediate need of vascular fluid in serious wound shock must necessarily make the alimentary ingestion of fluid a secondary therapeutic measure to intravenous injection.

VIII. Discussion.

A reduction in blood volume has been previously demonstrated by indirect methods in experimental shock. Dale and Laidlaw (10) drew attention to this fact in the shock-like condition produced by histamine. Both Govaerts (6) and Cannon (11) also considered that the relatively high hæmoglobin found so often in cases of wound shock was due to a decrease in blood volume. Actual estimations of the total blood volume by the vital red method have demonstrated

a consistent reduction in this series of cases. However, that the reduction in blood volume is secondary to some still unknown primary cause seems evident. One result of the action of this primary etiological factor is the fact that the vascular system is unable to retain the normal amount of plasma ; and if this condition persists for any considerable period of time, the vascular system loses its ability to retain fluid, as shown in the cases G. W. W. and A. H., Table IV. In contradistinction to conditions of shock, we do know that the blood volume under normal conditions remains remarkably constant and that changes are quickly adjusted. This adjustment of the blood volume in normal subjects is maintained by a constant intake and output of certain constituents through the semipermeable walls of the smaller blood vessels. Thus, it is clear that the blood vascular system is in most intimate relation with the tissues, and cannot be considered as an isolated closed system of tubes. Then again, the problem of shock is bound up with that of hæmorrhage, for in both there is a definite loss of fluid from the circulation. The present investigation of wound shock has been directed mainly towards the quantitive changes that take place in blood and plasma volume. In pure hæmorrhage of moderate degree the blood volume is almost immediately restored. That this restoration of volume may not be entirely due to the addition of fluid to the plasma, but also to a temporary increase in red blood corpuscles, is suggested by the results obtained in the donor G. G., Table I, and in the case J. McP., Table III. For an early temporary increase in total hæmoglobin after hæmorrhage could be explained if there was a reserve of red blood cells for immediate use of the body. The idea of a reservoir of red blood corpuscles has been the subject of considerable investigation, and Lamson (12) was able to show that in experimental polycythæmia, resulting from large doses of epinephrin, the great increase in the number of red cells depended upon the hepatic circulation remaining intact. If the hepatic artery was ligatured before the injection of epinephrin, the blood volume decreased, but the usual marked rise in red cells did not take place (13). These experiments pointed to the liver as a reservoir of red blood cells and suggested that the latter could be washed into the general circulation under certain abnormal conditions. However, this fact remains clear that when hæmorrhage is severe or is accompanied by extensive trauma, as in wound shock, a condition develops in which the normal process of blood volume restoration fails to take place.

In shock without hæmorrhage the reduction in blood volume ndicates a marked disturbance of the normal mechanism by which the blood volume is maintained. When considering the loss of fluid from the blood stream the question of the body's intake and output of fluid is of importance. With a certain degree of shock, fluid supplied to the body will cause an increase in blood volume. But in graver states of shock the smaller vessels of the vascular system are unable to retain an adequate amount of fluid. This altered condition of the small blood vessels also suggests an explanation for the inability to absorb fluid. Further knowledge is needed as to the cause of this alteration in the peripheral vessels, which appears to be a common feature in many shock-like conditions.

IX. Summary.

1. Reduction of total blood and plasma volumes are striking and important features in wound shock.

2. Decreased blood volume in wound shock is the result of a cause yet undetermined.

3. The actual volume of circulating blood must be considered when interpreting the red blood corpuscle count and the hæmoglobin percentage.

4. In shock without hæmorrhage there is a reduction in blood volume, but not to such a degree as when hæmorrhage also has occurred. With a blood volume below 75 per cent. the patient shows serious symptoms of shock; when it is below 65 per cent. his condition is critical.

5. After moderate hæmorrhage without shock the blood volume is rapidly restored.

6. Cases of wound shock can be divided into three groups, depending upon clinical symptoms and blood volume reduction.

7. Recovery from wound shock is associated with an increase in blood volume, which may take place with or without intravenous infusion of blood or gum-saline solution. The initial partial restoration of blood mass is due to a large increase in plasma volume.

8. Deaths that occur in cases of wound shock cannot always be credited to shock itself; frequently they are due to early bacterial infection, to which condition shock may be considered a predisposing factor.

9. An important factor in the treatment of serious cases of wound shock is to increase the amount of fluid in the circulation. For this purpose intravenous infusion is essential.

10. In certain cases of severe wound shock the blood-vessels are incapable of retaining an adequate amount of fluid in the circulation.

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Name	Age	Weight in kilos		Blood volume % body wt.	Plasma volume c.c.	Plasma volume % body wt.	Medication	Remarks
W. G.	19	65	4.	..	3,710			
				..	3,820			
			5.	..	3,420	..	1,900 c.c. fluid only since bleeding	
		65	11.	..	3,660			

Name	Age	Weight in kilos		Blood volume % body wt.	Plasma volume c.c.	Plasma volume % body wt.	Medication	Remarks
F. E. C.	19	56	2	71	2,240	80		
				..	..	..	Amputation rt. hand, lt. lower arm; 1,100 c.c. glucose and bicarb. sod. per rectum in 24 hours	Hæmorrhage during operation considerable
		53·5	2	77	2,650	99		
			2	..	..	..	.. ..	Evacuated 30.v.18
M. M.	28	73	1	64	2,525	69	.. ..	Large hæmatoma in lt. thigh
		73	1	71	3,025	83		
		70	1	77	3,375	96		
		70·5	2	80	3,710	106		
		70·9	2	89	3,730	105		
			3					
		68·2	6	96	3,440	100	.. ..	Evacuated 7.vii.18
J. A.	24	55	8	..	..	..	.. ..	X-ray shows large lt. hæmathorax
				72	2,200	80		
			9					
			11	..	2,680			
		53·6	14	..	2,720	..	1,150 c.c. fluid containing blood aspirated lt. chest	
			15	..	2,820			
			19					
		51·8	22	96	2,820	109	.. ..	Evacuated 23.viii.18
R. F.	26	56		77	2.385	85		
				..	..	..	Excision of wound; ligation of temporal art.	
				..	..	..	.. ..	Evacuated 5.ix.18

TABLE I

DONOR FOR BLOOD TRANSFUSION

Name	Age	Weight in kilos	Date	Wound	Time after wound	Hæmorrhage		Pulse rate	Resp. rate	Blood pressure		Blood								Medication	Remarks
												W.B.C.	R.B.C.	Hgb.	Hæmatocrit	Blood volume	Blood volume % body wt.	Plasma volume	Plasma volume % body wt.		
					hours	Ext.	Int.			Systol.	Diastol.			%	%	c.c.		c.c.			
				Donor for transfusion																	
W. G.	19	65	4.viii.18	Before bleeding	..	..	..	60	20	118	78	8,000	5,400,000	86	37	5,890	..	3,710			
				880 c.c. blood removed from vein—																	
				1 hour after bleeding	..	..	..	60	18	120	80	10,000	5,000,000	80	37	6,060	..	3,820			
			5.viii.18	24 hours after bleeding	..	..	..	64	20	100	65	9,000	4,600,000	82	35	5,260	..	3,420	..	1,900 c.c. fluid only since bleeding	
		65	11.viii.18	7 days after bleeding	..	..	..	68	20	120	75	6,000	4,100,000	80	32	5,380	..	3,660			

TABLE II

RECOVERY WITHOUT INTRAVENOUS THERAPY

Name	Age	Weight in kilos	Date	Wound	Time after wound	Hæmorrhage		Pulse rate	Resp. rate	Blood pressure		Blood								Medication	Remarks
												W.B.C.	R.B.C.	Hgb.	Hæmatocrit	Blood volume	Blood volume % body wt.	Plasma volume	Plasma volume % body wt.		
					hours	Ext.	Int.			Systol.	Diastol.			%	%	c.c.		c.c.			
F. E. C.	19	56	23.v.18	G.S.W. both lower arms	10½	++	..	120	20	70	40	29,000	4,100,000	80	34	3,400	71	2,240	80		
					13½	..	..	116	20	85	60										
					15	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Amputation rt. hand, lt. lower arm; 1,100 c.c. glucose and bicarb. sod. per rectum in 24 hours	Hæmorrhage during operation considerable
		53·5	24 v.18	.. ..	39	..	..	104	22	100	55	15,000	3,000,000	60	24	3,490	77	2,650	99		
			27 v.18	.. ..	..	..	..	78	20	100	55	..	..	..	..	..	..	..	..	.. ..	Evacuated 30.v.18
M. M.	28	73	15 vi.18	Comminuted fracture of lt. femur; skin unbroken	11½	..	+++	120	20	70	50	22,000	5,100,000	83	37	4,000	64	2,525	69	.. ..	Large hæmatoma in lt. thigh
		73	16.vi.18	.. ..	36	..	..	100	20	90	60	17,000	4,800,000	74	31	4,420	71	3,025	83		
		70	18.vi.18	.. ..	84	..	..	96	16	120	70	11,000	4,200,000	63	26	4,560	77	3,375	96		
		70·5	21.vi.18	.. ..	156	..	..	72	20	125	70	18,000	3,100,000	..	22	4,760	80	3,710	106		
		70·9	26.vi.18	.. ..	..	..	..	96	..	115	60	10,000	4,300,000	68	31	5,400	89	3,730	105		
			30.vi.18	.. ..	..	..	..	84	..	..	..	10,000	4,900,000	81	33						
		68·2	6.vii.18	.. ..	..	..	..	76	..	115	65	9,000	5,000,000	97	38	5,550	96	3,440	100	.. ..	Evacuated 7.vii.18
J. A.	24	55	8.viii.18	Thro' and thro' bullet wound lt. chest; large lt. hæmathorax	22	..	+++	120	26	60	45	..	..	..	..	..	..	..	..	.. ..	X-ray shows large lt. hæmathorax
					24	..	..	112	24	70	40	17,000	4,000,000	87	35	3,385	72	2,200	80		
			9.viii.18	.. ..	42	..	..	112	20	105	70										
			11.viii.18	.. ..	90	..	..	112	20	105	70	15,000	3,400,000	69	26	3,540	..	2,680			
		53·6	14.viii.18	.. ..	162	..	..	110	22	100	70	9,000	3,500,000	69	25	3,620	..	2,720	..	1,150 c.c. fluid containing blood aspirated lt. chest	
			15.viii.18	.. ..	186	..	..	110	22	115	75	17,000	3,500,000	69	25	3,760	..	2,820			
			19.viii.18	.. ..	..	..	..	76	..	110	60	13,000	4,200,000	74	31						
		51·8	22.viii.18	.. ..	..	..	..	100	24	105	70	12,000	4,700,000	83	33	4,210	96	2,820	109	.. ..	Evacuated 23.viii.18
R. F.	26	56	1.ix.18	Thro' and thro' bullet wound face; temporal art. cut	13½	++	..	124	20	95	70	26,000	4,700,000	91	35	3,670	77	2,385	85		
					19½	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Excision of wound; ligation of temporal art.	
			2.ix.18	.. ..	34	..	..	..	..	110	75	..	..	81	..	..	..	..	..	.. ..	Evacuated 5.ix.18

TABLE III

RECOVERY WITH INTRAVENOUS THERAPY

Name	Age	Weight in kilos	Date	Wound	Time after wound	Hæmorrhage		Pulse rate	Resp. rate	Blood pressure		Blood							Medication	Remarks
												W.B.C.	R.B.C.	Hgb.	Hæmatocrit	Blood volume	Blood volume	Plasma volume	Plasma volume	
					hours	Ext.	Int.			Systol.	Diastol.			%	%	c.c.	% body wt.	c.c.	% body wt.	
M.	29	66·4	2.viii.18	G.S.W. rt. lower leg	6½	++	..	120	20	110	75	10,000	4,300,000	83	32	4,500	80	3,060	92	
					7	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Excision of wound
					11	..	..	114	16	98	60									
			3.viii.18	.. ..	32	..	..	102	20	125	75	..	..	..	..	..	..	..	..	Amputation of rt. leg at knee; infusion 600 c.c. 4 % sod. bicarb.
		58·6	8.viii.18	.. ..	..	..	..	88	18	105	45	13,000	2,000,000	..	20	4,500	..	3,600	..	.. ..
S.	33	62·7	11.v.18	G.S.W. lt. groin; G.S.W. rt. lower leg; lt. femoral vein cut	11	+++	..	112	16	65	?									
					12½	..	..	?	..	?	?	31,000	4,500,000	83	33	3,120	58	2,090	66	Infusion 500 c.c. 6 % gum
					13	..	..	112	..	70										
					15	..	..	?	20	45	..	..	..	..	..	..	..	..	..	.. ..
					16	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
					21	..	..	120	16	60	40									Transfusion 450 c.c. blood; excision of wounds; infusion 500 c.c. 6 % gum, 600 c.c. 4 % sod. bicarb.
			12.v.18	.. ..	34	..	..	134	20	85	60									
			13.v.18	.. ..	58	..	..	114	16	115	75									
			14.v.18	.. ..	..	..	..	96	16	120	75	..	..	58	21	4,350	..	3,440		
		62	17.v.18	.. ..	..	..	..	96	16	115	70	..	..	62	25	4,350	..	3,260	..	.. .. Evacuated 17.v.18
W. B.	19	62·7	26.iv.18	Penetrating wound abdomen; multiple wounds, legs	3½	++	+	112	16	95	60									
					5	..	..	112	..	80	55	11,000	5,400,000	97	42	3,830	72	2,220	69	
					6	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Laparotomy; 4 perforations of bowel; infusion 600 c.c. 6 % gum
					8	..	..	112	28	80	45									
			27.iv.18	.. ..	22	..	..	120	16	130	85	..	..	..	..	..	..	..	..	Excision of wounds lt. knee and rt. ankle
			28.iv.18	.. ..	46	..	..	116	20	130	85									
			29.iv.18	.. ..	70	..	..	96	20	140	85									
			8.v.18	.. ..	..	..	..	120	20	120	60	27,000	3,100,000	57	23	4,075	..	3,135	..	.. .. Rt. ankle still discharging pus; evacuated 9.v.18
E. P. W.	35	65	30.iv.18	G.S.W. both legs; lt. femoral art. cut	12	..	..	92	24	100	65	21,000	4,500,000	90	40	4,250	77	2,550	78	
					12½	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Excision of wounds; infusion 600 c.c. 6 % gum
					18½	..	..	130	16	90	60									Muscle shows evidence of gas gangrene in both wounds
			1.v.18		31	..	..	116	18	115	75									
			3.v.18	.. ..	..	..	..	120	26	110	75	8,000	3,400,000	68						
			6.v.18	.. ..	..	..	..	88	24	100	45	..	..	..	..	..	..	..	..	.. .. Evacuated 6.v.18

[Continued on next page.

TABLE III—RECOVERY WITH INTRAVENOUS THERAPY (*continued*)

Name	Age	Weight in kilos	Date	Wound	Time after wound	Hæmorrhage		Pulse rate	Resp. rate	Blood pressure		Blood								Medication	Remarks
												W.B.C.	R.B.C.	Hgb.	Hæmatocrit	Blood volume	Blood volume % body wt.	Plasma volume	Plasma volume % body wt.		
					hours	Ext.	Int.			Systol.	Diastol.			%	%	c.c.		c.c.			
A. E. K.	19	58·2	20.vi.18	G.S.W. rt. lower leg; fracture of tibia and fibula	10½	+++	..	124	24	75	40	29,000	4,200,000	76	32	2,680	54	1,820	62		
					15	..	..	130	24	60	40	..	..	..	..	..	..	..	..	Infusion 500 c.c. 6 % gum	
					18	..	..	136	18	80	60										
					20	..	..	124	20	90	55	..	..	..	..	..	..	..	..	Amputation rt. leg at knee; infusion 500 c.c. 6 % gum	Weight of lower leg 5 kilos
					22	..	..	112	20	90	60										
		52	21.vi.18	.. .. ..	38	..	..	108	20	110	60	..	..	52	22	2,950	67	2,300	88		
			22.vi.18	.. ..	57	..	..	96	20	135	75										
			23.vi.18	.. ..	87	..	..	96	20	135	70										
		51	25.vi.18	.. ..	..	..	..	92	24	110	55	12,000	2,700,000	35							
			30.vi.18	.. ..	..	..	..	72	..	..	..	11,000	3,200,000	54	24						
		48	6.vii.18	.. ..	..	..	..	64	..	110	60	9,000	..	58	25	3,700	90	2,780	116		
		47·3	10.vii.18	.. ..	..	..	..	84	..	100	55	8,000	..	66	30	3,810	94	2,670	113		
		46	20.vii.18	.. ..	..	..	..	80	..	105	60	9,000	..	76	32	3,600	92	2,450	106	.. ..	Evacuated 21.vii.18
W. H. P.	30	61·4	12.vii.18	Multiple G.S.W.	13	+++	..	140	26	85	55	19,000	5,100,000	91	36	3,125	60	2,000	65		
					13½	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Infusion 800 c.c. 6 % gum	
					18½	..	..	124	24	95	70	..	..	..	..	..	..	..	..	Amputation rt. leg at knee; excision of other wounds	
					23½	..	..	128	22	90	60	15,000	..	..	29	3,380	..	2,400			
		55·4	13.vii.18	.. ..	37	..	..	120	24	115	70	13,000	..	46	19	3,360	..	2,715			
			14.vii.18	.. ..	..	..	..	120	22	130	70										
		54	15.vii.18	.. ..	..	..	..	120	20	115	70	8,000	..	35	16	3,570	..	3,000	..	.. ..	Temp. 101·2°; infection lt. ankle; W.B.C.; differential smear; P.M.N. 87 %
		51	19.vii.18	.. ..	..	..	..	124	..	120	65	14,000	..	40	17	3,840	..	3,190			
		47·3	26.vii.18	.. ..	..	..	..	120	..	115	65	25,000	..	42	20						
			27.vii.18	.. ..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Amputation lt. foot	Weight of foot 1·8 kilos
		40	13.viii.18	.. ..	..	..	..	108	..	110	65	9,000	..	59	26	3,850	..	2,850	..	.. ..	Evacuated 15.viii.18
P. G. C.	24	69	27.viii.18	G.S.W. lt. leg and lt. knee; G.S.W. rt. foot	12	+++	..	120	20	120	70	16,000	3,250,000	67	24	3,685	63	2,800	81	.. ..	Culture from lt. leg + for gas gangrene infection
					12½	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Infusion 550 c.c. 6 % gum	
					14	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Amputation above lt. knee; excision wound rt. foot	Weight lt. leg 6 kilos
					15	..	..	104	20	110	55										
					18	..	..	..	..	..	..	..	..	50							
					24	..	..	124	26	130	70	..	..	48							
		61·8	28.viii.18	.. ..	36	..	..	132	24	100	60	18,000	..	48	17	3,800	..	3,150			
			29.viii.18	.. ..	..	..	..	104	20	120	60	..	..	45							
		58·2	30.viii.18	.. ..	..	..	..	106	24	120	60	18,000	..	42	15	3,500	..	2,980			
		56·8	2.ix.18	.. ..	..	..	..	102	22	120	55	9,000	..	36	14	3,675	..	3,160	..	.. ..	Evacuated 3.ix.18

[*Continued on next page.*

TABLE III—RECOVERY WITH INTRAVENOUS THERAPY (*continued*)

Name	Age	Weight in kilos	Date	Wound	Time after wound	Hæmorrhage		Pulse rate	Resp. rate	Blood pressure		Blood								Medication	Remarks
												W.B.C.	R.B.C.	Hgb.	Hæmatocrit	Blood volume	Blood volume % body wt.	Plasma volume	Plasma volume % body wt.		
					hours	Ext.	Int.			Systol.	Diastol.			%	%	c.c.		c.c.			
W. E.	21	60	10.viii.18	Traumatic amputation both feet, G.S.W.	9	+++	..	126	24	55	40	33,000	3,500,000	69	25	2,670	52	2,000	66		
					9½	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Infusion 625 c.c. 6 % gum	
					10	..	..	126	..	80	60										
					11	..	..	132	26	60	35	..	..	..	..	..	..	..	..	Amputation of legs above stumps; infusion of 600 c.c. 6 % gum	Weight of limbs amputated 3·2 kilos
					15½	..	..	?	..	..	..										
					22	..	..	108	20	105	60										
		54·5	11.viii.18	.. ..	33	..	..	108	20	115	65	..	..	38	16	3,240	70	2,725	100	Since ad. 24 hours; 4,000 c.c. saline per rectum	
		51	12.viii.18	.. ..	..	..	..	94	..	120	70	..	..	30	14	3,620	84	3,115	122		
		48·6	13.viii.18	.. ..	..	..	..	120	..	120	70	..	..	29	12	3,540	85	3,115	128		
			14.viii.18	.. ..	..	..	..	96	..	110	60	14,000	..	25	11	3,585	86	3,190	131		
		48·2	16.viii.18	.. ..	..	..	..	96	..	120	75	..	..	29	12	3,310	80	2,910	121		
		48	20.viii.18	.. ..	..	..	..	100	..	110	65	..	..	28	14	3,750	91	3,225	134		
		46	24.viii.18	.. ..	..	..	..	108	..	120	65	..	..	33	15	3,650	93	3,100	135		
			28.viii.18	.. ..	..	..	..	96	..	105	60	..	..	36	15	..	..	..	..	.. ..	Evacuated 29.viii.18
J. McP.	33	67	8.viii.18	G.S.W. rt. side penetrating chest and abdomen	10	..	+	72	24	120	70	19,000	6,000,000	106	43	6,180	109	3,525	105		
					11	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Laparotomy through chest wall and diaphragm	300 c.c. blood in rt. chest and peritoneal cavity
			9.viii.18	.. ..	34	..	..	88	24	120	70	16,000	..	100	43	5,330	94	3,040	91		
		63	14.viii.18	.. ..	..	..	..	100	20	115	75	25,000	..	102	42	4,570	85	2,650	84		
		60	19.viii.18	.. ..	..	..	..	128	..	100	80	25,000	..	106	42	4,760	93	2,760	92	Adhesions in rt. chest freed	Culture chest fluid + non-hæmolytic streptococcus
			20.viii.18	.. ..	8 hrs. after opern.	..	..	160	..	60	40	..	..	..	..	..	..	..	..	2,200 c.c fluid removed; infusion 600 c.c. 6 % gum	
					18 hrs. after opern.	..	..	120	..	100	75	..	..	80							
		59	21.viii.18	.. ..	42 hrs. after opern.	..	..	120	..	120	65	19,000	..	62	26	4,810	95	3,560	121		
		59	25.viii.18	.. ..	..	..	..	96	..	120	70	18,000	..	64	26	4,810	95	3,560	121		
		60	31.viii.18	.. ..	..	..	..	96	20	115	65	11,000	..	71	27	4,630	91	3,380	113	.. ..	Evacuated 1.ix.18

TABLE IV

FATAL CASES

Name	Age	Weight in kilos	Date	Wound	Time after wound	Hæmorrhage		Pulse rate	Resp. rate	Blood pressure		Blood							Medication	Remarks
												W.B.C.	R.B.C.	Hgb.	Hæmatocrit	Blood volume	Blood volume % body w.	Plasma volume	Plasma volume % body wt.	
					hours	Ext.	Int.			Systol.	Diastol			%	%	c.c.		c.c.		
Mc. L.	21	64	13.v.18	Abdomen, penetrating	9	++	+++	116	40	85	55	20,000	4,600,000	75	36	3,125	58	2,310	72	
					13	..	..	136	32	90	60	..	..	..	..	..	..	..	..	Laparotomy; transfusion 450 c.c. blood	900 c.c. blood in peritoneal cavity
			14.v.18	.. ..	42	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.. ..	Died; autopsy—peritonitis
M. N.	37	69	28.v.18	Abdomen, penetrating	8	..	+++	100	22	70	50	6,000	5,000,000	83	36	3,594	62	2,300	66	
					10	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Laparotomy; resection of bowel; infusion 6 % gum sol. 1,000 c.c.	1,000 c.c. blood in peritoneal cavity
					15	..	..	120	24	80	50	..	4,000,000	..	31	4,400	80	3,037		
			29.v.18	.. ..	26	..	..	112	30	110	85									
			31.v.18	.. ..	80	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.. ..	Died; peritonitis
A. G.	35	60	29.v.18	Abdomen crushed; no external wound	3	..	++	80	..	50										
					10	..	..	96	..	85	60	21,000	4,900,000	80	42	4,310	84	2,488	83	
					11	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Laparotomy; liver torn	500 c.c. blood in peritoneal cavity
			30.v.18	.. ..	30	..	..	108	22	115	60	15,000	4,700,000	..	38	3,974	79	2,364	78	.. ..	Blood plasma and urine suggest bile pigment
		56	1.vi.18	.. ..	75	..	..	128	36	90	55	16,000	..	..	31	3,090	6	2,130	76	.. ..	Scleræ jaundiced
					80	..	..	132	36	75	40										
					86	..	..	..	..	..	..	..	..	..	..	..	..	..	..	No intravenous injections	Died; autopsy—laceration of liver; 600 c.c. blood-tinged fluid in peritoneum
J. Br.	33	62	4.vi.18	Bullet wound thro' and thro' rt. lower leg; post. tibial art. cut	9	+++	..	96	20	50	35	20,000	3,600,000	..	31	3,000	57	2,070	67		
					11	..	..	140	..	50											
					12	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Amputation rt. leg	
					12½	..	..	..	..	..	..	..	..	..	..	..	..	..	..	No intravenous injections	Died; autopsy—œdema of lungs; no other abnormal lesions
M. L.	36	70	..	G.S.W. lt. lower leg; post. tibial art. cut	8	+++	..	90	16	45	30	39,000	3,700,000	70	31						
					8½	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Transfusion 800 c.c. whole blood	
					11½	..	..	104	14	80	55										
					13½	..	..	104	16	55	..	..	..	..	..	..	..	..	..	Amputation lt. leg; infusion 600 c.c. sod. bicarb. 4 %, 500 c.c. gum 6 %	
					14	..	..	104	20	85	50										
					16	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.. ..	Died; autopsy—œdema of lungs; all organs very moist
A. H.	19	54	6.vi.18	G.S.W. both lower legs	7½	..	..	128	20	75	40	36,000	5,800,000	81	33	2,540	55	1,700	63		
					10½	..	..	136	18	80	60	..	..	..	..	..	..	..	..	Transfusion 880 c.c. whole blood	
					11½	..	..	120	20	130	85	..	..	..	32	2,690	59	1,830	68	Amputation rt. lower leg	Clinical improvement striking
					12	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.. ..	Died; autopsy—œdema of lungs; all organs very moist

[*Continued on next page.*

TABLE IV—FATAL CASES (*continued*)

Name	Age	Weight in kilos	Date	Wound	Time after wound	Hæmorrhage		Pulse rate	Resp. rate	Blood pressure		Blood								Medication	Remarks
												W.B.C.	R.B.C.	Hgb.	Hæmatocrit	Blood volume	Blood volume % body wt.	Plasma volume	Plasma volume % body wt.		
					hours	Ext.	Int.			Systol.	Diastol.			%	%	c.c.		c.c.			
R. J.	19	72	20.vi.18	G.S.W. rt. lower leg; fract. tibia and fibula	13	+++	..	124	28	55	..	30,000	3,700,000	65	28	3,380	56	2,435	68		
					16	..	..	140	24	95	60										
					17	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Amputation rt. lower leg; infusion 500 c.c. 6 % gum, 500 c.c. 4 % sod. bicarb.	
			21.vi.18	.. ..	34	..	..	112	18	100	35										
	64		22.vi.18	.. ..	58	..	..	112	20	105	40	30,000	..	40	17	4,012	74	3,380	104	.. ..	Blood culture, hæmolytic streptococci
			23.vi.18	.. ..	82	..	..	128	20	100	50										
			24.vi.18	.. ..	110	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.. ..	Died; autopsy—early broncho-pneumonia
J. A.	22	61·4	1.vii.18	Fractured pelvis; no external injury	5	..	+++	?	24	35	..	21,000	5,100,000	80	31	2,870	55	1,980	64	.. ..	Heart rate 80
					12½	..	..	116	24	60	40										
					13½	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Infusion 500 c.c. 6 % gum	No physiological response; fracture of pelvis
					17	..	..	..	..	..	..	..	..	..	..	..	..	..	..	... ..	Died; autopsy—rt. int. iliac art. cut; large extra-peritoneal clot; blood lost 1,000 c.c.
W. D. C.	33	74·5	11.vii.18	G.S.W. both thighs; rt. hæmothorax	8½	++	+++	116	24	75	55	..	..	..	..	..	..	..	..	.. ..	X-ray chest—large rt. hæmothorax
					12½	..	..	120	28	80	55	36,000	6,000,000	115	45	4,020	63	2,210	60		
					13½	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Excision of thigh wounds; no large vessel severed	
					17½	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Infusion 850 c.c. 6 % gum	
			12.vii.18	.. ..	20	..	..	120	44	75	50	..	5,200,000	87	28	4,100	65	2,950	79		
					28	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.. ..	Died; autopsy—900 c.c. blood rt. chest; œdema lungs; gas gangrene rt. thigh; culture +
J. Bt.	22	61	17.vii.18	G.S.W. lt. groin	8	+++	..	140	28	55											
					9	..	..	..	..	..	..	22,000	5,200,000	81	32	3,000	58	2,030	67		
					10½	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Infusion 1,000 c.c. 6 % gum	
					11½	..	..	..	..	?	..	..	3,100,000	..	23	3,180	61	2,450	81	.. ..	Heart rate 130; resp. irregular
					11¾	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.. ..	Died; autopsy—œdema of lungs; lt. ext. iliac art. cut; large extra-peritoneal hæmatoma
N. V. C.	23	62	18.vii.18	G.S.W. head, penetrating	?	..	..	120	26	105	70	29,000	5,200,000	85	33	2,985	56	2,000	64	Excision of wound tract	Pt. unconscious
			19.vii.18	.. ..	..	..	..	160	48	85	45	..	..	68	25	3,288	62	2,466	80		
			20.vii.18	.. ..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	No intravenous injections	Died; autopsy—multiple fractures of skull; lacerated brain

Continued on next page.

TABLE IV—FATAL CASES (*continued*)

Name	Age	Weight in kilos	Date	Wound	Time after wound	Hæmorrhage		Pulse rate	Resp. rate	Blood pressure		Blood							Medication	Remarks
												W.B.C.	R.B.C.	Hgb.	Hæmatocrit	Blood volume	Blood volume % body wt.	Plasma volume	Plasma volume % body wt.	
					hours	Ext.	Int.			Systol.	Diastol.			%	%	c.c.		c.c.		
C. K.	22	71·4	29.vii.18	G.S.W. lt. side, penetrating	7	+	++	100	32	110	70	13,000	5,800,000	102	40	5,180	85	3,110	84	
					8½	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Laparotomy; 500 c.c. blood in peritoneum	F.B. passed thro' lt. diaphragm, spleen, and upper pole lt. kidney; bowel uninjured
					17	..	..	114	34	85	55									
			30.vii.18	.. ..	28	..	..	..	..	..	..	..	..	..	..	..	..	..	..	No intravenous injections	Died; autopsy—œdema rt. lung; lt. lung collapsed; early peritonitis
L. L.	29	74·5	2.viii.18	G.S.W. both thighs; lt. femoral art. and vein cut	16½	+++	..	140	20	65	45									
					17	..	..	..	..	..	..	36,000	3,900,000	71	34	3,790	60	2,500	68	
					17½	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Infusion 575 c.c. 6 % gum	
					19	..	..	..	26	60	40	..	..	..	..	..	..	..	..	.. ..	Heart rate 160
					19½	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Infusion 575 c.c. 6 % gum	
					20	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Excision of wounds; infusion 600 c.c. 4 % sod. bicarb.	Gas gangrene in lt. thigh
					22	..	..	140	26	80	50									
			3.viii.18	.. ..	38	..	..	120	16	110	55	..	..	..	..	..	..	..	..	Amputation lt. thigh	
					44	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Infusion 570 c.c. 6 % gum	
			4.viii.18	.. ..	58	..	..	140	26	70	30	22,000	2,000,000	32	15	..	..	..	..	Transfusion 880 c.c. blood	
		65	5.viii.18	.. ..	82	..	..	124	22	120	65	16,000	2,500,000	45	18	4,284	78	3,515	108		
					94	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.. ..	Died; autopsy—gas gangrene lt. thigh: culture+; œdema of lungs
G. R. H.	25	68·2	12.viii.18	G.S.W. rt. lower leg; shell-gas poisoning	6½	++	..	132	26	95	60	19,000	4,900,000	85	36	4,240	73	2,800	82		
					7	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Excision of wound	
			13.viii.18	.. ..	24	..	..	130	40	110	70	..	..	..	..	..	..	..	..	.. ..	Signs of consolidation over rt. lung
			14.viii.18	.. ..	48	..	..	..	..	..	..	..	..	..	..	..	..	..	..	No intravenous injections	Died; autopsy—tracheal lesions due to mustard gas; broncho-pneumonia; œdema of lungs
S. S.	19	..	11.viii.18	Severe wound shock; no gross wound	6	0	0	?	..	..	..	..	..	..	..	..	..	..	..	Infusion 600 c.c. 6 % gum	
			12.viii.18	.. ..	42	..	..	128	28	105	80	11,000	6,300,000	125	..	..	..	..	..	.. ..	Very restless
					43	..	..	?	30	..	..	..	..	..	..	..	..	..	..	.. ..	Heart rate 106
					46	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.. ..	Died; autopsy—no gross ext. or int. hæm.; small hæm. into pancreas and mesentery
G. W. W.	25	76	1.ix.18	Bullet wound, abdomen, penetrating	8½	..	++	84	24	130	75	12,000	5,400,000	104	46	5,910	91	3,190	84		
					9½	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Laparotomy	500 c.c. blood in peritoneum; 3 perforations of bowel; fracture of ilium; heart rate 148
			2.ix.18	.. ..	24½	..	..	?	28	60	45	..	..	120	..	..	..	..	..	Infusion 550 c.c. 6 % gum	Vomiting; very restless; heart rate 148
					27½	..	..	?	36	65	45	..	..	..	..	..	..	..	..	Infusion 550 c.c. 6 % gum	Heart rate 128
					29½	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.. ..	Died; autopsy—general œdema of subcut. tissue; œdema of lungs; pleural effusion

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THE SENSE OF STABILITY AND BALANCE IN THE AIR

BY

HENRY HEAD, M.D., F.R.S.

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Introduction.

The faculty in man, which has raised him to a dominant position in the animal kingdom, is his capacity to make use of tools. He projects his powers of appreciation to the extremity of some mechanical contrivance, manœuvred by hand or foot, and so enormously extends his power to influence objects at a distance from his body. When we probe a wound or use a stick to explore the ground, we 'feel' at the end of the rod, not in our fingers. From such comparatively simple acts we can rise to the most complicated adjustments of eye and hand. For example, when shooting, our eyes are fixed on the bird passing across the field of vision; the gun is then thrown up with a movement so exactly regulated in time and direction, that the shot will arrive at a certain spot at the precise moment when the flight of the bird brings it to that position in space. We do not 'aim' or calculate some hypothetical distance 'in front'; nor do we actually see the gun at all. We carry out a reaction exactly adapted to the information given by our eyes. The more automatic this response the more likely is it to succeed in bringing down the bird.

Man not only uses this power of projecting himself to the end of some mechanical appliance in his work, but games were invented to exercise this faculty. Flying a machine heavier than air is nothing more than an extended application of this power, demanding adapted movements of every part of the body and limbs. No new elements come into the mechanical problems of flying that are not evident in riding a motor-bicycle, game shooting, cricket, or golf.

The vast majority of young men can acquire any of these aptitudes. A small minority are so constituted that they cannot do so; they 'do not feel safe' on a bicycle, and 'cannot hit the ball'. Such persons are rare amongst the healthy members of the community; but they form a small group who are 'not fond of games'. At the other end of the scale stand a small number of super-men, who seem to have been born with a natural gift, which rapidly carries them to a position above the average of their fellows.

Amongst candidates for the R.A.F. our aim must be to exclude those who are congenitally incapable of flying. At the same time we cannot hope to pick out super-men. We are concerned with the average youth who is capable of adjusting himself to conditions in the air. Any healthy young man, who is able to ride a motor-bicycle and play cricket or lawn-tennis well, can be taught to fly.

Were this the whole problem it would not be difficult to select suitable candidates. But it must not be forgotten that the R.A.F. is a fighting force. A man must not only be a good chauffeur, but he must be able to fight. I examined a pilot,

who was acknowledged to be a remarkable aviator capable of flying any machine and apparently fearless in the air. But he was sent back from France because he could not fly over the lines. On the other hand, I have come across pilots with a fine fighting record, who were not good flyers in the technical sense, and neither knew nor cared anything about the details of their machine.

At first, candidates for the flying branches of the two services were admitted after a medical examination which varied greatly in strictness. But, with the coming of the Military Service Act, the rush of volunteers greatly increased. This enabled the authorities to raise the standard of the medical examination; but at the same time its aim was somewhat extended. An attempt was made, not only to exclude those who showed signs of pathological states, organic or functional, but to select men who would be able to fly well.

The various functions which come into play during aviation were analysed, and methods were devised to test the physiological activities on which they were supposed to depend.[1] At the same time the importance of the abnormal states induced by flying at high altitudes led to the invention of simple cardio-vascular and respiratory tests, which were found to be of value in appraising the general medical condition of a candidate or flying officer.

In its final form the medical examination of the Candidates Board was intended to fulfil a threefold object:

(1) To exclude all who suffered from pathological conditions. These included, not only gross defects of the heart, lungs and nervous system, but also such functional defects as 'nervous instability'.

(2) Some persons of normal constitution are liable to suffer in the air from certain grave disabilities, such as 'giddiness' and 'fainting'. These states are no more evidence of a pathological condition than is sea-sickness or inability to swing without discomfort. It was hoped that by applying tests which made a call on the activity of the semicircular canals, muscular sensibility and other fundamental sensory functions, it would be possible to exclude candidates who would suffer from these disabilities in the air.

(3) A certain proportion of pupils are rejected because they have difficulty in learning to fly; they are 'heavy on controls', 'make bad landings', or 'have no air feeling'. It was hoped that tests, founded on the sensations underlying balance, would exclude candidates who might show these defects.

On the protocol (Form C.B. 7) of the R.A.F. Commissions Board are three headings, 'Nervous Stability', 'Muscle Sense' and 'Vestibular Stability'; it is with these we are mainly concerned in the first part of this report.

Unfortunately these portions of the schedule have been filled up with the conclusions arrived at by the examiner, without any

[1] All the tests for balance were invented and carried out by Arthur H. Cheatle, F.R.C.S., who directed the Otological work of the Candidates Board.

definite record of the tests employed. In actual practice his opinion was based on the following methods of examination:

(1) The '*Nervous Stability*' of a candidate was judged from his past history, revealed by a few direct questions; by the evidence of nail-biting, tics or other signs of want of control, such as tremor of the hands and inability to balance a rod on a flat board with the eyes open.

(2) The condition of the '*Muscle Sense*' was estimated by the manner in which he balanced a rod on a flat board with his eyes closed and by his capacity to stand on one foot for 15 seconds under the same conditions.

(3) As tests of '*Vestibular Stability*' the candidate was asked to walk along a line heel to toe and to turn completely on one foot, so as to face in the opposite direction. The character of the entry under this heading was also determined by the manner in which he stood on one foot with his eyes closed.

Thus it is obvious that three mechanical tests were habitually relied on to give the information required. First, the candidate was made to extend his arms and hands to see if he was steady or tremulous. Then he was made to stand on one foot for 15 seconds and then on the other, both with the eyes open and shut; he was also made to walk along a line and turn at the word of command. Thirdly, he was made to balance a rod on a flat board by means of each hand in turn, with his eyes open and shut.

But, before any conclusion can be reached concerning the correlation of these tests with ability to fly, the results must be recorded in terms of the actual methods employed. No general opinion should be given such as 'Muscular Sense defective'; the actual facts of the examination must be recorded.

Unsteadiness, when standing on one foot with the eyes closed, was supposed to represent want of 'Muscle Sense'. I therefore examined a number of pilots and pupils, who were unable to carry out this test on either foot, for their power of recognizing passive movement at the various joints of the lower extremities. Now we know from other lines of research that this is the most delicate of all the measurable tests for what is usually called 'Muscle Sense' or 'Deep Sensibility'. So fine is the power of perceiving passive movement at all the joints from the great toe to the hip, that the normal individual can appreciate without difficulty a range of 1° or even less. This is scarcely perceptible to the eye and yet its direction can be accurately described by any intelligent person. Amongst the pilots and pupils who were unable to stand on one foot with the eyes closed, I did not find a single one who could not appreciate 1° of passive movement at all the joints of the lower extremity. It is obvious, therefore, that in the class of young men with whom we have to deal, inability to carry out this test has nothing to do with defective 'Muscle Sense', but is due to lack of motor control or want of resolution.

The condition of 'Muscle Sense' in the upper extremities is supposed to be revealed by the manner in which the rod is balanced on a board, when the eyes are closed. I have carefully

measured the power of recognizing passive movement in a series of pilots and pupils who were unable to carry out this test; records from the joints of fingers, wrist, elbow and shoulder, showed that they had no difficulty in appreciating a movement of 1°. Evidently, in the class of case from which our material is drawn, failure to carry out this test has nothing to do with defective 'Muscle Sense'.

'Vestibular Stability' is estimated by the power to walk along a line, to turn on one foot and to stand on one leg with the eyes closed. But there is no evidence to show that any of these acts bears a direct relation to the activity of the semicircular canals. Moreover, I have examined four pilots who were intensely giddy and vomited in the air, none of whom had the least difficulty in carrying out these tests perfectly.

Before any progress can be made in our knowledge of abnormal conditions of balance in the air, all such headings as 'Muscle Sense', 'Nervous Stability', and 'Vestibular Stability', must be abolished, and the records should show the results of the actual tests employed. Then only will it be possible to obtain statistical evidence of their relation to flying capacity.

Chapter I. The Tests and what they reveal.

Although success or failure in these tests does not reveal the state of the 'Muscle Sense' or extent of 'Vestibular Stability', they form a valuable guide to the patient's physical and mental condition. I shall therefore consider these different methods of examination one by one, pointing out under what circumstances they are capable of yielding useful information. The material at my disposal consisted of 30 cadets, in 22 of whom I was able to obtain the after history; 20 pupils who were rejected for some inability to fly of a non-medical nature; 30 cases where a pilot or observer came to me on account of some disability such as vomiting or fainting in the air. In addition I have gained much useful experience from the patients under my care who passed through the annexe to the R.A.F. Central Hospital (Oakhill House).

1. *Tremor.*

When a young man is made to hold his hands out in front of him, and at the same time to protrude his tongue, any considerable tremor is a sign of some definitely abnormal condition. A tremulous tongue may be indicative of chronic indigestion or of alcoholic excess; unsteadiness of the fingers, especially when they are abducted and brought together again, is a certain sign of lack of control. Tremor is not so much an indication of a neuropathic temperament as of a definite disturbance of function. It is not surprising therefore that Major Bowdler concluded that the group which contains 'tremor' showed a high correlation with want of aptitude to fly. He found that out of 54

candidates who were accepted in spite of 'marked tremor', 14 did not qualify, a ratio of success to failure of 2·8 to 1. Amongst 2,000 candidates who showed no abnormal signs 7·6 per cent. only were ultimately rejected.

The number of completely normal young men who show tremor of the hands must be extremely small. In every case of a pupil, pilot, or observer that has come under my notice, this sign has been associated with some obvious cause. In a certain number it was due to alcoholic excess, and it was particularly evident in those pilots who took alcohol in order to be able to carry on their work. But, apart from alcohol, it is one of the commonest signs of stress of war service and was particularly frequent in those candidates who had already served in the infantry at the front. It was almost universally present in those officers who were admitted to hospital for some functional psychosis ('Shell Shock').

Tremor of the hands is a not infrequent sequel to malarial infection; it is more evident in delicate and precise movements, such as shaving, and the handwriting may be affected. Such unsteadiness comes out particularly well when attempting to balance the rod on a flat board.

Excessive smoking, especially the perpetual misuse of cigarettes, is responsible for much tremor of the hands in members of the R.A.F.

Thus, tremor is evidence of some disordered functional state, and should be looked for definitely in the course of the routine medical examination of candidates or pilots. It will be found most commonly amongst those who have been sent back from the front on account of stress of service, exhaustion, or states of anxiety.

2. *The Knee-jerk.*

The condition of the knee-jerk is of little importance in the class from which the candidates for the R.A.F. are drawn. They are all young. None of them have reached the age at which syphilis is likely to have attacked the mechanism of this reflex, and 'exaggerated' knee-jerks are of little significance. Major Bowdler could find no evidence that any flying disability was associated with 'exaggerated reflexes'.

A condition not infrequently called 'exaggerated knee-jerks' is, however, an indication of loss of general control, but has in reality nothing to do with tendon reflexes. Sometimes on tapping the knee the whole body is thrown into agitation and the patient may even cry out. If the knee is carefully watched, the true knee-jerk is seen to precede the general commotion. This 'exaggerated knee-jerk' is in reality an uncontrolled reaction to a gentle blow and the same person will be found to start at a sudden noise. This 'general response' to tapping the knee is a valuable sign of loss of control, but is no indication of the condition of the deep reflexes. It is usually associated with a state of anxiety and is more likely to be found in unfit pilots than in candidates for the R.A.F.

3. *Walking a line heel to toe and turning on one foot.*

The result of this test is recorded by the Examining Board under the heading of 'Vestibular Stability'. But there is nothing to show that inability to walk a line and to turn on one foot is evidence of anything more than clumsiness in action or slowness of comprehension.

We examined a number of cadets, all of whom had been passed by the Candidates Board and had already begun to fly. We were able to obtain the ultimate history in 22 cases; 13 flew well and amongst them 9 could walk a line and turn on one foot well, but 4 carried out this test badly. Amongst the 9 pupils who failed to qualify, 3 walked and turned well, whilst 6 were bad at this test.

Such numbers are useless for any statistical comparison; but certain points came out on closer personal examination of those who failed. One pupil showed astonishing lack of comprehension of the task he was asked to perform; when told to turn on one foot only, he walked round in a circle and repeatedly turned in this way, although we demonstrated to him the manner in which we wished him to carry out the test. This man did 6 hours and 25 minutes dual flying; but when the time came to go up alone, he 'went sick' and did not fly again.

The same failure to comprehend what was required was apparent to a less degree in two other cases amongst the pupils who were finally rejected. It has nothing to do with want of stability, but is evidence of a slow response to unexpected verbal commands.

Another cadet, who had fought successfully in France, found considerable difficulty in walking heel to toe and turning on one foot. He ultimately became an excellent scout pilot, but confessed that he disliked dancing. In fact it seems to us that this test is more likely to show ability to dance than any capacity to fly.

But whatever relation it may bear to flying it is certainly not evidence of 'Vestibular Stability'. For, out of 8 pilots who suffered from profound giddiness associated with vomiting in the air, two only failed to pass this test; both of these men were tremulous and showed other neuropathic signs and symptoms.

4. *Standing on one foot for* 15 *seconds with the eyes closed.*

If a candidate is unable to carry out this test, his failure has been attributed to defective 'Muscle Sense'. But I carefully tested the power of recognizing passive movements at the various joints of the lower extremities in several R.A.F. pilots and pupils, who failed to stand on one foot with the eyes closed. I selected the grossest cases only; but in no single instance was the power of recognizing posture and passive movement affected. Moreover, these same persons, who were unable to stand on one foot, could do so with both feet on the ground even when the eyes were closed; Romberg's sign was completely absent, showing

that the impulses passing up the posterior columns of the spinal cord were not affected. There is no evidence, therefore, that inability to stand on one foot for 15 seconds with the eyes closed bears any relation to disturbed sensations from the muscles and joints, in the class of young men with whom we have to deal. Moreover, all the pilots and pupils who failed to carry out this test in spite of repeated attempts, showed considerable tremor of the hands and were evidently suffering from some neuropathic or psychopathic condition.

Amongst the cadets who ultimately proved to be successful pilots, two carried out this test poorly. Both showed some tremor of the hands, and one of them had come home after fighting in France to join the R.A.F. Of the nine unsuccessful cadets, three showed defective power of standing on one foot, and of these two had distinct tremor of the hands.

Amongst 20 healthy pilots who were rejected on account of inability to fly and not for any physical reason, 15 carried out this test perfectly. Of the five who could not stand on one foot for 15 seconds on the first attempt, three were able to do so on a second trial and two only failed three times on each foot.

But amongst 20 pilots who came under my care for some pathological condition, such as vomiting or fainting in the air, fatigue, or anxiety, 11 showed gross defects in carrying out this test. Thus if we place together in one group the unselected cadets and the officers who had been rejected for defective flying capacity, we obtain 42 healthy individuals; amongst them were 10 cases where this test could not be carried out perfectly. On the other hand, of 24 pilots and pupils who ceased to fly because of some morbid condition in the air, 15 showed considerable difficulty in balancing themselves on one foot.

Thus it is evident that amongst candidates, pupils, and pilots of the R.A.F., inability to stand on one foot with the eyes closed for 15 seconds is evidence of some want of control and is not due to defective 'Muscle Sense'.

Secondly, this test is more likely to be badly executed by those who show other signs and symptoms of fatigue or anxiety, whether temperamental or acquired. It is not directly a test for flying capacity; but a man who has difficulty in carrying it out successfully will probably be found to be suffering from mental or physical stress. This will ultimately affect his handling of machines heavier than air, although it may have no influence on his work as an airship pilot.

To stand on one foot with the eyes closed for 15 seconds requires not only perfect automatic control but some determination. One of the respiratory tests invented by Colonel Flack also calls for a certain amount of resolute effort, and it is interesting to notice the frequency with which the results of the two methods fall together. The pilot under examination is told to blow into a U-tube and to support a column of mercury 40 mm. in height for as long as possible. Forty seconds is taken to be normal, although a healthy young man usually greatly exceeds this period. But the result is gauged not only by the time but also by the effect on the patient; if he becomes suffused and dis-

tressed he is considered to have failed even if he slightly exceeds 40 seconds.

Amongst 20 pilots who suffered from some abnormal condition in the air, 9 failed to pass both the balancing and U-tube tests. One showed defective power of standing on one foot, but supported the mercury for 45 seconds; one other failed in the respiratory test, but succeeded in balancing himself on one foot.

This association between the results of the two methods of examination might have been anticipated. Both depend on sustained effort, and anything which diminishes the power of concentration will influence both tests. All the 9 pilots who failed were suffering from fatigue, anxiety, want of sleep, bad dreams, or other analogous symptoms; it is such states which above all others are associated with defective concentration and diminished control.

5. *Balancing a rod on a flat board with the eyes open or closed.*

This is an easy test to carry out and requires no apparatus that cannot be improvised out of the lid of a cigar-box and a small tuning-fork with a flat base. The board is placed on the table with the rod standing upright on that part further from the person to be examined. He is then asked to grasp the edge nearest to him with his fingers, to raise the board to the level of his shoulders and to replace it on the table without upsetting the rod. Should he fail at the first attempt with either hand, he is allowed to try three times in succession. He is then examined in the same way with the eyes closed.

Failure to balance the rod with the eyes open was assumed by the Examining Board to be evidence of want of 'Nervous Stability', a heading shared with Tremor, Tics, and other symptoms of want of control. But inability to pass this test, with the eyes closed, was classed as due to defective 'Muscle Sense'.

I therefore selected for closer investigation several of the worst cases, where the subject of examination failed entirely to balance the rod with either hand, when his eyes were closed. In no instance could I find any measurable defect in 'Muscle Sense'; 1° of passive movement could be accurately appreciated at all the joints of the upper extremity. It is evident, therefore, that, amongst pilots and candidates of the R.A.F., failure to balance the rod with the eyes closed is not dependent on lack of Muscular Sensibility. It is, in fact, simply another and more severe method of examining the same want of control and clumsiness of action, betrayed by balancing the rod with the eyes open.

Most normal persons find greater difficulty in balancing a rod on a flat board with the eyes closed than when they are open. Now, whenever some function of the nervous system is defective, the more complex and difficult task shows evidence of failure before one that is simpler and easier of execution. It is not surprising, therefore, to find that out of 20 cadets who had already begun flying, 4 showed some difficulty in balancing

the rod with the eyes open and 8 with the eyes closed ; but this difficulty bore no relation to their subsequent career as aviators. Moreover, amongst 20 pupils rejected solely because of inability to fly, 5 had some difficulty in balancing the rod with the eyes open, 10 with the eyes closed. Thus if we compare the normal cadets and rejected pupils there is nothing to show that there was any material difference in behaviour between those who could and those who could not fly, provided they were physically healthy.

But when we turn to the 25 pilots or pupils who suffered from abnormal symptoms in the air, the proportion of failures was nearly double as great; 13 had difficulty in balancing the rod with the eyes open, 19 with the eyes closed. Evidently this test reveals some condition common amongst those who have suffered from pathological states in the air. But provided the individual is otherwise healthy, it does not bear any direct relation to flying capacity.

On looking through the records of those who failed more or less grossly in this test, the high proportion of cases of tremor is at once evident. This might have been anticipated ; for any tremor makes it difficult to carry out an operation which requires a steady hand. Out of 28 pilots who had suffered from pathological states in the air, 14 were tremulous and all but one showed difficulty in balancing the rod on the board. In the same way, out of 50 cadets and rejected pupils 11 showed some tremor of the hands, and all of these failed to balance the rod satisfactorily.

But it must not be supposed that this test is only another means of discovering tremor. Amongst 28 pathological cases there were 7 persons who were not tremulous but could not balance the rod with normal certainty. In the same way, amongst 30 cadets and 20 rejected pupils, 9 could not carry out this test satisfactorily, though free from tremor. In almost every instance of this class I made a special note that the failure was due to erratic conduct, carelessness, want of resolution, or defective comprehension of the task and the best method of carrying it out. In other cases the movements were 'clumsy' and 'stiff', or the subject seemed 'utterly worn out' and 'tired'.

Thus we may conclude that provided the subject of examination is in perfect physical health, this test has no direct bearing on his capacity to fly a machine heavier than air. But, on the other hand, it is a useful method of detecting states of exhaustion, flying-stress, insomnia, and other neuropathic and psychopathic conditions, in an early stage of development. There is no difference in principle between the test carried out with the eyes open or shut. The latter is a more difficult task, and therefore tends in most cases to show defects sooner than when the balance is guided by sight.

6. *Conclusions.*

Some of the methods of examination discussed in this chapter are of sufficient value to form part of the routine medical

examination of candidates and pilots of the R.A.F. Tremor of the hands and tongue must always be carefully noted. The candidate should be asked to stand first on one leg and then on the other for 15 seconds with the eyes closed. He is also made to balance a rod or tuning-fork on a flat board with either hand in turn, first with the eyes open and then with them closed. He is allowed three attempts, and the character of his failure to carry out this test should be recorded, if possible.

In every case the actual method of examination must be recorded, and all such general categories as 'Muscle Sense', 'Vestibular Stability', and the like, must be avoided. The vast mass of material collected by the Candidates Board is rendered almost worthless from lack of this obvious precaution.

With such material as we meet with in the R.A.F., consisting as it does of young men in whom gross organic disease is almost absent, these tests reveal the condition of physiological or psychical control. Such control may be defective from innumerable causes; some of the most potent are fatigue, physical or mental stress, anxiety and fear. All of these conditions may appear in the course of the work of any aviator, but were enormously aggravated by flying under war conditions.

Chapter II. 'Giddiness', Vomiting, and 'Fainting' in the Air.

1. *Introduction.*

A pilot may lose control and become unconscious in the air from many various causes. Of these want of oxygen at high altitudes is perhaps the best known, and has formed the subject of several previous Reports. It is not my intention to deal with this condition, but to consider abnormal symptoms which may occur at any height and are not due to physical or chemical deficiencies in the atmosphere.

These are usually called by the sufferer 'giddiness', 'dizziness', and 'fainting in the air'. Unfortunately many medical men record them as 'vertigo' and 'syncope', without any qualification or explanatory statement of what actually happened. Nothing could be more fatal for the progress of knowledge than this widespread tendency to translate popular nomenclature into nosological language. To say that an aviator suffered from 'vertigo' inevitably suggests that the cause of his trouble was the semicircular canals, whilst 'syncope' attracts attention to the cardio-vascular system.

Throughout this chapter I shall allude repeatedly to the way in which the patient reacts when rotated in a chair. American workers have laid great stress on this response to rotation, and have carried out their observations in such a way that each group of semicircular canals is stimulated in turn. In fact, this method of examination formed, at one time, the determining test for admission to their Flying Service. A candidate was

obliged to react in a certain manner or he was not accepted. The Report of the American Surgeons states—

'It was decided to reject applicants whose vestibular apparatus gave evidence of motion-sensing acuity below a certain degree, albeit it was fully recognized in establishing this limit, that it in no way represented a line of demarkation between acuities of this perception compatible with and incompatible with flying.'

The extent of the response of the vestibular apparatus to disturbances of equilibrium was estimated in two ways. First, the candidate was rotated with his head in a strictly regulated position and the duration of the nystagmus was measured. Secondly, without rising from the chair and with his eyes still closed, he attempted to find the observer's finger, which was placed in a certain, previously familiar, position. If the deviation to this test did not reach a certain amount the candidate was assumed to be endowed with less than the normal vestibular acuity; if, on the other hand, it exceeded certain limits, arbitrarily fixed, he was rejected as over-sensitive. But this method of examination is purely empirical, and the data obtained have not so far been correlated with ability to fly.

I have not attempted to check these results; for throughout this work I have used the rotating chair, not as a method of measuring the response of the semicircular canals, but as a means of inducing an abnormal reaction. A healthy man responds in a certain way to rotation, although the degree of giddiness varies greatly. But in certain persons, who suffer from morbid phenomena in the air, the reaction is abnormal and excessive. It is frequently possible, by rotation, to induce physiological states and sensations analogous to those experienced in the air; the disability can be reproduced in a minor form. This is true, not only in cases of 'giddiness', but also in those where the pilot has 'fainted' in the air.

When we sit upright in a chair, the horizontal canals are not strictly in a plane parallel to the ground; they are slightly tilted and the head must be inclined to about 30° before they become strictly horizontal. But this is not the natural position; the head is usually carried so that the eyes look directly forwards and not on to the ground. This is the posture to which we are adapted in daily life, and the head can be turned rapidly to the right or left without giddiness or abnormal symptoms; for these movements occur more frequently than any others under natural conditions. And yet at no time, either during this static pose or on lateral deviation, are any of the semicircular canals in a position suitable for exclusive physiological stimulation. If we want to test the response of the horizontal canals specifically, the head must be suitably adjusted before rotation; but if, as is my intention, we wish to study the general functional reaction of the patient, he must be placed in the natural position seated upright in the chair.

It is important to understand the different aims of the two methods of carrying out this test. Those who carefully place the head in such a posture, that each set of canals is stimulated in

turn, look to the specific nature of the physiological response. On the other hand, I was anxious to determine, not the afferent results of such stimuli, but the way in which the patient could adapt himself to somewhat violent sensory impressions. My object was to examine his control in face of disturbances of equilibrium. Similarly, I not infrequently tested his reaction to a slight blow on the knee or to a sudden noise.

When a healthy man is rotated ten times in twenty seconds with his eyes closed, the results depend mainly on the position of the head. I have not attempted to modify its posture so as to stimulate any one set of semicircular canals alone; but the patient was directed to sit upright in the chair, as if he was gazing directly forwards. On opening his eyes the room seems to be going round in a direction opposed to that in which he was rotated. A normal man is not giddy, and suffers from no nausea, headache, or other discomfort.

If he is asked to rise and walk forwards he may tend to deviate, but rapidly recovers himself and reaches the table, five paces in front of him, without difficulty. When the chin has been held somewhat downwards, so as to bring the one set of canals strictly into the horizontal position, this deviation tends to take place in the direction of the rotation. But with the head in the erect position this is not the case in most instances; thus rotation clockwise is usually followed by more or less deviation to the left.

It is most important to record all rotation, actual or apparent, in terms of the long axis of the body and not as movements to the right or left. But deviation on rising from the chair is described as 'to the right' or 'to the left', because this is the only movement that can be actually observed, although the patient is often aware that it is the expression of a rotatory sensation.

In all my cases the patient was first turned 10 times in 20 seconds clockwise. Then, after a pause, varying in length according to the severity of the reaction, he was rotated in the opposite direction. Usually this second stimulation produced a somewhat greater effect than the first, particularly in subjects who showed other evidence of some abnormal condition.

2. *Giddiness associated with temporary abnormalities of the Auditory Apparatus.*

In order that we may be able to adapt ourselves to changes in position the auditory apparatus must be structurally sound. This is assured in most cases by the careful examination of candidates before they are accepted into the R.A.F.

But Sydney Scott[1] has pointed out that giddiness and other allied symptoms may occur in aviators who are unable to obtain a free and immediate passage of air through the Eustachian

[1] *Journ. of Laryngology, Rhinology, and Otology*, Feb. 1919. Vol. XXXIV, No. 2, p. 51. A fuller account of these researches is about to be published as a Report of the Air Medical Investigation Committee.

tubes. The ears may be normal, but the pilot suffers from a cold in the head. The air no longer passes freely through one or both Eustachian tubes and, when he rises to a considerable height or descends with great rapidity, an abnormal condition of tension is produced in one or both middle ears. This, acting on the vestibular apparatus, evokes intense giddiness and is accompanied by pain of more or less severity. Not infrequently effusion, or even haemorrhage, occurs into the middle ear.

Most experienced pilots are conscious of the salutary effect of swallowing during a rapid descent, and habitually chew gum for this purpose. But, in some cases, a temporary condition of the nose or throat may make it impossible to regulate the tension within the middle ear, with disastrous results to the pilot.

In the following instance the giddiness occurred whenever the patient caught a cold in the head, although his auditory apparatus was otherwise normal.

Case No. 1. 2nd Lieut., aged 19.

He first went into the air in September 1917 and had flown for 13 hours solo on Avros before he felt any discomfort. In December 1917 he caught cold, when sleeping in a canvas hangar with snow upon the ground. He went up one morning, with a cold in the head, and suddenly 'felt dizzy'; his head seemed 'to be whizzing round inside', and he 'felt strange'. He went up frequently during the next few days and was 'giddy' on several occasions. He did not vomit and was not nauseated. Throughout this period he was deaf.

He went away on leave, and recovered entirely. On returning to his squadron, he flew solo for 9 hours in perfect comfort, and graduated on April 9, 1918.

He was then transferred to another squadron to fly service machines. Here he caught another cold, and one day, when in the air, whilst suffering from headache and running at the nose, he felt himself becoming giddy at 3,000 feet. He shut off his engine, but does not know how he came down. He was flying an Avro and, according to the report of his Wing Commander, started to spin. He stalled the machine at about 30 feet, and broke some struts in landing, but was not hurt.

He was seen by me in September 1918, four months after the last occasion on which he had been in the air.

He was then a well-built young man with somewhat narrow nostrils. He had been operated on successfully for adenoids at the age of 11 years, and there was no obvious abnormality in his throat or nose. His hearing was good, and the membranes were normal and not retracted; but he said that, whenever he caught a cold, something went wrong with his ears.

Respiratory and cardiac tests showed no gross abnormality, but his balance on one foot was bad. He failed three times in succession to stand on the right foot for 15 seconds, and succeeded with difficulty in doing so on the left. He balanced the rod on the flat board at the first attempt with the right hand, when his eyes were open, and on the second attempt with the left hand. But with the eyes closed, he failed altogether to carry out this test with the left hand, and only succeeded on the second attempt with the right. And yet, on testing his power of appreciating passive movement, he could recognize 1° at all joints of both upper and lower extremities.

When he was rotated, he did not deviate definitely in either direction, and touched the spot on the table perfectly. But he complained that, as soon as he rose from the chair, he felt as if he was 'moving backwards and

forwards'. He seemed to move 'first from right to left, and then back again from left to right'. The window in front of him 'seemed to be doing the same, wavering backwards and forwards'. He was not giddy, and felt perfectly normal, as soon as the 'wavering' passed off. There was no nausea or headache.

From this case there is an easy transition to such a one as the following, where the throat was in an obviously abnormal condition.

Case No. 2. Lieut., aged 27.

He joined the R.F.C. in June 1917, and went to France on January 31, 1918, flying S.E. 5. He began to notice that, when coming in after high scouting, he was a little deaf in the left ear. When he descended from a height, he had to 'blow up his ears', and 'sometimes they would stay plugged for three or four days'.

On April 3, 1918, whilst coming home to the aerodrome, he got into a backwash and went 'dizzy'. He spun from 4,000 feet to 2,500 feet, but did not lose consciousness. He knew what was happening, pulled his machine out of the spin and followed the others home. On alighting from his machine, the giddiness continued for some time.

I saw him nine days later and his tonsils were red and swollen, the left more so than the right. The membranes were normal, and he was not then deaf.

Both these cases are examples of the ill-effects produced by uncorrected changes of tension within the auditory apparatus. Sydney Scott has shown, from careful examination of a large number of pilots at the front, that such abnormal conditions in the middle ear are amongst the commoner causes of giddiness in the air. A healthy man is suddenly exposed to unnatural stimulation of the essential sensory mechanism due to uncorrected tension in the auditory apparatus; he responds in a normal manner with a more or less acute vertigo. Here it is not the reaction of the individual or the response of his semicircular canals that are in fault, but the abnormal and unequal tension in the middle ear.

But 'giddiness' may occur in aviators apart altogether from such external stimuli. In such cases their abnormal state in the air must be due to one or two causes. Either the sensory impressions evoked by changes of bodily posture must be excessive, or the general resistance to the uncontrolled acceptance of such impulses must be profoundly diminished. This defective power of integration and control may be acquired or constitutional. Such cases are of profound diagnostic and scientific importance, and form the subject of the next two sections of this chapter.

3. *Giddiness in the Air with no abnormal conditions in the Auditory Apparatus.*

Most healthy persons can be made giddy, provided the rotatory movement is sufficiently violent, and especially if the head is held in some abnormal position. This reaction is not a patho-

logical condition; it is a normal response to an acute disturbance of equilibrium. But the ease with which it can be evoked varies greatly; some, in childhood, were not able to swing without discomfort and were sick on a train journey. As they grew up, however, this response was evoked less easily, and, provided the stimulus was not unusually severe, they differed little from their fellows.

In the same way many normal men become giddy when first exposed to rapid changes of posture in the air. After a few turns the instructor carries out some aerobatic evolution and, when first looped, rolled, or spun, many pupils become uncomfortable and a certain number vomit. But the majority rapidly recover and may become expert and bold aviators. They have adapted themselves to the new conditions; the stimuli from the peripheral end-organs no longer dominate the field of response. They are controlled or suppressed, not by the will, but by that power of adaptation which is one of the most potent factors in the activity of the central nervous system. In the course of evolution the lower centres have come increasingly under the dominance of those of higher functions and more recent development. Actions, which in lower animals can be carried out by the spinal cord alone, become impossible in man without the co-operation of the centres in the mid-brain.

Even in the fully developed nervous system of man the acquisition of some new aptitude is associated with an increasing control of higher centres. We learn to adapt ourselves to the conditions around us and cease to be the victims of unco-ordinated sensory impressions.

In order that any of these acquired aptitudes may be carried out in a perfect manner attention must be concentrated on the end and object of the movement, and the motor act must become as nearly as possible automatic. A man shoots his best when his eye is fixed on the bird and he is not conscious of his gun. In the same way an aviator must be able to concentrate on the evolution he wishes to perform and carry out the necessary acts automatically. To turn a corner on a bicycle or to bank an aeroplane 'you just lean over' and the desired change occurs without further thought. The man who flies by verbal rules is a bad pilot and will certainly come to grief.

Anything which diminishes the power of concentration tends to lessen control over the reaction of the lower centres to sensory stimulation. An attack of influenza, a 'crash', domestic worry or fear, all act in the same direction. A pilot who was giddy when he first went into the air, but recovered completely, may fall back to his original mode of reaction and be unable to carry out any aerobatic evolution. Such persons are no longer normal, not because the response is a pathological one, but because, for a time at any rate, they have been reduced to a lower level of functional efficiency.

My first example is that of a perfectly healthy man, who never recovered from the tendency to become giddy and to vomit in the air. The case is an instructive one, because he succeeded in concealing his disability and was only saved from death in France

by the prompt assistance of two colleagues. Moreover, since he was marked unfit for flying, he has repeatedly been in the air as a passenger during the course of his work, and appreciates exactly the conditions which render him uncomfortable.

Case No. 3. Capt., aged 23.

After serving in the Infantry he was transferred to the R.F.C. and began to fly on June 15, 1917. He graduated in October and went to France as a Scout pilot on November 14, 1917, flying Sopwith Camels. He did 150 hours in the air, of which 50 were in France.

The first time he was taken into the air on an Avro he vomited at about 2,000 feet. So long as he flew straight he managed without difficulty, but when he turned rapidly or 'threw the machine about' he was attacked with nausea and occasionally vomited. By coming down whenever he was uncomfortable, and by doing as little 'stunting' as possible, he managed to conceal his disability and was sent out to France after 80 hours in the air.

Here he felt no discomfort at first, because his duties consisted mainly of patrolling at about 10,000 feet. One day, however, he was attacked by the enemy and compelled to turn rapidly in the air; this caused him to vomit severely. He was so ill that he could not look about him, and the enemy were on his tail, firing into his machine before he realized what had happened. Two of his companions saved him and drove off the Germans. On coming down safely he was obliged to go to bed for two or three hours. He went up three times after this adventure, but vomited on each occasion and was sent home.

As a child he disliked swinging, and was easily made sea-sick. At the age of 14 he was swung upon a gate and was so sick that he was obliged to go to bed.

I saw him on his return from France. He was well built, strong, and healthy. He seemed so completely normal that I took him to the Candidates Board, and the examiners kindly put him through all the tests for me without asking any preliminary questions. He passed without qualification.

When, however, he was rotated in the chair the general reaction was excessive, although the visible response was normal in character. After ten turns clockwise, he rose and deviated to the right; the room seemed to be moving in a direction opposed to that in which he had been turned. After a pause of ten minutes, he was rotated counter-clockwise; he then staggered to the right and to the left unsteadily, whilst the room seemed to go round with the hands of the clock. This response was not abnormal, but the general reaction was disproportionately great. He was attacked with profound nausea, his face and hands sweated, and he said he felt exactly as he does in the air.

He was a highly-trained scientific student and was therefore given employment in the Technical Department. In the course of his work he frequently goes into the air as a passenger, and suffers from no discomfort so long as the flight is steady. But on one occasion recently he was up in a D.H. 9 with a B.H.P. engine, which gives off unpleasant fumes near the observer's face; the air was 'bumpy', and the combination of the two conditions caused him to vomit.

This is an example of a perfectly normal man, who has never been able to adapt himself to disturbances of equilibrium. The actual response to rotatory stimuli was normal in character, but the reaction it evoked was excessive.

The next case is one where the profound reaction to change of posture was one aspect only of a congenital want of nervous control, in a man of unusual physical strength and athletic ability.

Case No. 4. 2nd Lieut., aged 23¾.

He served for three years in the Infantry, and gained his commission from the ranks. He was splendidly built and had been a professional football player; but he had always noticed that if he looked up as he ran, he became giddy and tended to fall.

It is interesting to notice that, in spite of his build, appearance, and fighting record, he had always been 'nervous'. As a child he could not sleep without a light and was terrified of the dark. He always dreamt unpleasantly, and on waking 'saw big ugly faces' in the room. This occurred frequently up to the age of 16. During the last twelve months his unpleasant dreams had recurred; they mostly took the form that he was with the Infantry, and that 'they were in a tight place'.

After joining the R.A.F. he noticed that he did not suffer in the air so long as he flew straight, but turning made him giddy. He was most uncomfortable when the nose of the machine was put down, but banking always upset him. After several trials he was finally rejected as permanently unfit for pilot or observer.

This man's behaviour to the usual tests was in striking contrast to those of No. 3. He could not support himself for 15 seconds on either foot with the eyes closed. He failed altogether to balance the rod on the flat board, either with the eyes open or closed. But he showed equally gross defects to the respiratory tests, and could not support 40 mm. of mercury for more than 30 seconds; his pulse-rate behaved in a normal manner throughout, showing that this failure was not due to any cardio-vascular inadequacy.

From previous experience of such cases, I suspected that he might react violently to rotation, and I therefore turned him five times only in each direction; an interval of five minutes elapsed between the two observations. On being rotated he became so giddy that he sat coiled up clinging to the arms of the chair, unable to move. He did not even attempt to rise, but said he felt extremely ill, exactly as when he was in the air.

This is an example of an excessive reaction to sensory stimulation, due to lack of central control. In spite of his unusual physical development, this man was endowed with a psychopathic temperament, and the response to unusual stimulation of the vestibular apparatus was manifested in the form of a minor anxiety neurosis.

The next case shows that a pupil who starts with giddiness and vomiting in the air may overcame his disability and develop into an able pilot. But anything which diminishes general control may cause him to regress to his original condition.

Case No. 5. Lieut., aged 22.

After 3 years and 11 months in the Infantry he joined the R.F.C. During his first dual flight on an Avro he felt sick and vomited. He recovered entirely, quickly gained his wings, and went to France to fly Sopwith Camels. He had no giddiness, nausea, or other discomfort, even when 'stunting'.

But, after 90 hours war flying, he was shot down in aerial combat and chased from 9,000 feet by his opponent. On reaching the ground he found himself unhurt, but pinned under his machine, which had turned over.

Six days later he resumed flying and discovered that he had lost all confidence. He flew for 20 hours, but could not face the fighting and was sent home. After two months' rest he seemed to have recovered entirely, and was posted as instructor to a Training Squadron at home. He went up three times with the Wing Instructor and on each occasion vomited violently.

As a child he disliked swinging, and felt 'dizzy' and 'sick'. On a railway journey he cannot sit with his back to the engine without feeling 'squeamish'. All the members of his family react in the same way, both to swinging and to travelling by train.

The only one of the general tests which he carried out badly was balancing the rod with the eyes closed; he succeeded on the third attempt only with the right hand, and with the left failed altogether. He showed no excessive reaction to rotation; when turned ten times clockwise or counter-clockwise he deviated in the opposite direction, exactly like a normal person, but recovered himself quickly. The room seemed to be moving horizontally opposed to the direction of rotation. He did not suffer from nausea or any discomfort.

This was an instance when, in spite of an hereditary tendency to giddiness and nausea, the pilot adapted himself to the new conditions perfectly. But, with the shock of being shot down, he regressed, and all his old disability returned in spite of the fact that he was physically in perfect health.

In the following example the patient had a natural tendency to vomit in the air, but gained sufficient control to fly as an observer for more than three months in France and to take part in much aerial fighting. He suddenly regressed in consequence of acute fear.

Case No. 6. 2nd Lieut., aged 19.

He began his training in the air as an observer in April 1918 on a D.H. 4, and vomited three times in six flights. The nausea started about ten minutes after he left the ground with 'a drawing in the stomach up to the throat'; and as soon as he experienced this sensation he knew he must vomit. When it was over he felt better, and could go on flying comfortably.

The nausea came on apart from any aerobatic evolution; but when rolled, looped, or spun, he was 'dizzy' and 'sick' all the time.

He went to France as an observer and flew for $3\frac{1}{2}$ months in a Bristol Fighter, under war conditions. So long as he was not heavily 'stunted', he enjoyed his work and did not vomit. But, of all evolutions, rolling upset him most.

At the end of August 1918 he suddenly went to pieces under the following circumstances. His Squadron was going to take part in a combined attack during the afternoon. In the course of the morning a new pilot went up for a turn in the air and dived into the earth on the aerodrome, killing himself and his observer. Shortly afterwards a second pilot and observer were killed in the sight of the patient and his companions. But the pre-arranged military operation could not be postponed, and he was obliged to go up with his squadron the same afternoon. He was intensely frightened and vomited in the air. From that time onwards he was sick whenever he went up, even when flying straight; finally he was so ill that his pilot brought him back shortly after starting.

He could never swing as a child, because it made him giddy, and he always vomited in a train, and sometimes even in a tramway car. When

uncomfortable in the air his sensations were exactly those he experienced in childhood before he was sick in the train. He had often suffered from sea-sickness.

Physically he was in perfect health, and was not tremulous. He passed all the usual balancing tests, and had no difficulty in supporting 40 mm. of mercury by blowing for 40 seconds. The pulse did not react abnormally to this form of effort.

But when rotated in the chair his reaction was characteristic. Turned ten times clockwise, he rose, stood with his feet apart, leaning forwards, shaking. He did not deviate, but moved slowly and unsteadily directly forwards to the table. He said that the room was not going round, but that his 'feet seemed to be rocking'. 'I had the drawing feeling in my stomach up to my throat, that I know so well in the air.' After a pause of ten minutes he was rotated in the opposite direction with exactly the same result. He stood unsteadily, in the same attitude, with his feet apart, quaking as if in fear.

Here, a healthy young man, relatively over-susceptible to disturbances of equilibrium, succeeded in adapting himself sufficiently to carry out his work as an observer under war conditions. But, with the development of an anxiety neurosis, due to an acute state of fear, the physical reaction became severe and overwhelming.

In the following case the patient had never experienced any discomfort until he attempted to fly after an attack of influenza. He then became giddy and vomited repeatedly in the air.

Case No. 7. 2nd Lieut., aged 19½.

He thoroughly enjoyed flying from the first, and had never had an accident. He obtained his wings without difficulty and was preparing to go to France, when on June 30, 1918, he had an attack of influenza. He was in bed for ten days with no complications and then went on leave.

On July 27 he went up for the first time since his illness as a passenger and vomited at 1,500 feet. 'I was giddy; my eyesight seemed bleary and full of specks, and it was like a bad bilious attack.' He was so determined to conquer this feeling that he went up again the same day and again vomited. This was a simple straight flight in an Avro.

As a child he thoroughly enjoyed swinging, and he has never been sea-sick, even when fishing from a small boat.

I saw him at the beginning of September 1918 and he was then easily tired, even by a short walk. He had lost a good deal of weight since the attack of influenza, but there were no abnormal physical signs in the lungs or heart. The balance of his hands was poor, and he was unsteady when standing on one foot. He had considerable difficulty in raising the rod on the flat board, especially with the eyes closed. But the respiratory tests were fairly well carried out [U-tube 45 secs.], and the pulse did not react abnormally to effort.

When turned ten times clockwise, he rose, deviated slightly to the left, but touched the spot on the table without difficulty. The room seemed to be revolving in the direction opposite to the rotation. He said he felt giddy, and looked it. The reaction, when turned ten times counter-clockwise, was exactly analogous; he deviated to the right and the room seemed to be going in the same direction.

In neither case was the visible response abnormal. But its effect upon his general condition was excessive. Throughout the rest of the day he felt

sick; his appetite was not impaired, but he had a continuous feeling of nausea. He also complained of an abnormal sensation, as 'if something was pressing down in the back of my head'.

This seems to be a case where the response to rotation was not abnormal; but owing to the diminution of general resistance, due to influenza, normal sensory impulses evoked an unusual general reaction.

The next case illustrates how a flying officer, who had never known discomfort in the air, may become giddy and vomit as a sequel to a gastro-intestinal disturbance. It also shows the close relation between the two conditions 'vomiting' and 'fainting' in the air.

Case No. 8. 2nd Lieut., aged 29.

He began to fly in Canada in January 1918 and enjoyed it extremely. In June he was posted to a Squadron in England, and whilst there, during the first week of August, suffered from a short attack of diarrhoea. Throughout the four days of its duration he continued to fly, but felt so weak that he was forced to use two hands to the controls on steep turns; suddenly, at about 1,000 feet, he was attacked with 'dizziness' and thought he was about to vomit. After resting for a few days, he seemed to have recovered entirely and took two short flights without ill effects.

He was then posted to another Squadron and began to suffer from indigestion, with 'wind', 'cramps in the stomach', and 'some pain shortly after taking food'. He was given a laxative, and this started another attack of diarrhoea. He did not fly for a week, but on September 8, 1918, after 20 minutes in the air, he became 'dizzy'. His head seemed to 'swim', his vision became hazy, and at about 100 feet everything 'went black' for a few seconds.

After a good night's sleep he went up again next day and was perfectly comfortable, so long as he flew straight; but as soon as he began to circle round a ground target he became 'dizzy'. 'The target started going round with me.' He felt sick, broke out into a sweat, and repeatedly put his head over the side, partly because he was certain he was about to vomit, and partly in the attempt to obtain fresh air. He kept on swallowing and felt all would be right if thereby he could prevent something coming up from his stomach.

He has never been sea-sick, and could swing with pleasure as a child.

I saw him in October 1918. He was still suffering from flatulent dyspepsia; his bowels were opened once or twice daily, and the motions were always somewhat loose. The tongue was clean, the teeth were fairly good, and there was very slight gingivitis. There were no abnormal physical signs in the heart or lungs, but he had distinctly lost weight. He slept well, and did not dream unpleasantly.

He passed all the tests for balance without difficulty, but rotation in the chair produced a characteristic reaction. On turning him ten times clockwise, he rose, swayed with eyes half closed, and appeared dazed; but he stepped forwards and touched the table without deviating definitely in any one direction. He said: 'Things seem to start going to the right and yet I seemed to be able to control it by blinking. Everything went misty just as it does in the air, and my stomach felt funny.' On rotation in the opposite direction, he rose slowly and staggered to the right, pulled himself together and moved to the left, finally touching correctly. He said: 'This time it was more as if I could not get where I wanted and misjudged my

distance. I thought I was right on the point, when I was a long way off. This is just like my landings after an attack in the air.' He added that he felt 'squalmy' in the stomach.

In this case the abnormal reaction took at one time the form of giddiness and nausea, and at another time that of partial unconsciousness; it forms a transition to the next group, where the pilot is said to 'faint in the air' at low altitudes.

4. *'Fainting' in the Air.*

In the previous section I have described a series of cases where the reaction to disturbances of equilibrium took the form of giddiness and nausea. Another not uncommon abnormality is what is usually called 'fainting' in the air. A 'mist' or 'haze' comes before the eyes and 'all goes dark'. It is not an unpleasant sensation, and is said to resemble closely the early stage of an anaesthetic. This passes into complete insensibility and the pilot may fall forward on to his controls; but if he is strapped in sufficiently tightly his hands leave the stick and his feet no longer act on the rudder. Should he be spinning on a stable machine, he may come to himself some miles away flying on a level keel.

Case No. 9. 2nd Lieut., aged 20.

He began flying in February 1918, and obtained his wings in July of the same year. From the first moment he thoroughly enjoyed being in the air, and flew well without discomfort or difficulty.

But, in the middle of July 1918, he was in bed for two days with a short attack of influenza. Four days later he was flying an R.E. 8 when he 'felt faint' at 5,000 feet. He came to himself at about 1,500 feet, to find he was in a spin; he managed to right the machine, but broke an axle on landing.

I saw him in October 1918, after a prolonged period of leave and ground duty. He was then a healthy young man of rather poor physique. Heart and lungs were normal. He could sustain the mercury in the U-tube for 40 seconds. During this test his pulse volume became rather small and the tension poor; the rate, however, was in no way excessive, and recovery occurred within a normal period after the close of the effort. The balance tests were carried out perfectly.

Rotation produced a normal response. On turning ten times clockwise, he rose, deviated slightly to the left, but touched the spot on the table easily. He said he was giddy and that the room seemed to revolve against the hands of the clock, but he was not in any way uncomfortable. Turned in the opposite direction, he deviated slightly to the right; the room seemed to go the same way, but he recovered rapidly. He suffered from no nausea, headache, or other discomfort.

This is the case of a man of somewhat poor physical development who 'fainted' in the air after an attack of influenza.

The next example of this condition is a pilot with long experience and 250 hours war flying in France. He became chronically tired and, at the end of a long patrol, 'fainted' in the air.

Case No. 10. Capt., aged 20½.

He joined in August 1916, and went out to France as a pilot in December of that year.

In July 1917, after 250 hours flying under war conditions, he was returning from a long patrol when he 'fainted' in the air. But, knowing he was going on leave, he said nothing about it and came home on July 28.

After three weeks he was posted to a Training Squadron as instructor. He began to notice that he had lost all keenness for flying and that he 'started at a noise'. One day in December 1917 he was suffering from neuralgia in his face and went up in a D.H. 6. He 'came over foggy and silly', and became unconscious at about 4,000 feet. He 'woke up' at about 1,500 feet and flew the machine back to the aerodrome without difficulty.

He then went to hospital for a fortnight and, after three weeks' leave, returned to his Squadron feeling perfectly well. He was extremely keen and thinks he never taught better; he instructed thirteen pupils in a month. He was then transferred to another aerodrome, where he remained for four months. At the end of that time he found he could not stand 'stunting'.

In July 1918 he was given ground duty. He came before me in November because he was anxious to return to flying. He could walk 20 miles without discomfort, and had been playing two rounds of golf daily. At first he noticed that he was off his game; his normal handicap had been 4, he was now playing 8, though improving daily.

When I saw him he was in splendid physical condition, and passed all the respiratory and balance tests perfectly. On opening his eyes, after ten turns clockwise, the room 'seemed to take half a turn to the right and then stand still'. He rose, walked straight to the table and touched well. He added, 'It was just like coming out of a cloud; I felt I was going to pull out at once.' On being rotated counter-clockwise, his sensations were *mutatis mutandis* identical. He experienced no discomfort of any kind.

Evidently this was a case where 'fainting in the air' was associated with exhaustion, consequent on the strain of excessive flying under war conditions. It is interesting to record that this pilot had never 'crashed' since he obtained his wings.

The next case shows that 'fainting in the air' may be the terminal phase of a long period of loss of confidence.

Case No. 11. Capt., aged 27.

This pilot flew before the war in a training school, and was given his wings when he joined up in January 1916.

On July 20 of the same year he suddenly lost confidence under the following conditions. When taking a machine across country he was compelled to make a forced landing in a field. He tried several times to get out, but could not clear the surrounding trees. On landing, after the seventh attempt, he noticed twigs from the trees in the tail and under-carriage of this machine. This brought home to him how near he had been to disaster, and he became so frightened that he left his aeroplane and returned by train. Next day he tried to fly, but failed twice; every little bump 'set my heart going, and I used to wonder if I should come down again'.

He was discharged in August 1916; but in December he began to fly again as a test-pilot. In March 1917 he was given a commission in the

R.F.C., and flew so confidently and well that he was made Flight Commander to a Training Squadron.

On October 27, 1917, he went to France in charge of a section for issuing machines. On December 22 he was testing an S.E. 5, when he 'fainted' at about 5,000 feet. 'Everything seemed to go black all at once.' He recovered himself at about 1,000 feet, but lost consciousness again. He next remembers that he was on the ground, hanging upside down from the machine, which had turned over. He could not release his belt, but was not injured in any way.

After a short stay in hospital, and some months of ground duty, he began to fly again at the end of April 1918. He then became sleepless and frequently suffered from nightmares; these consisted of a recurrent dream that he saw a machine falling without wings. He was never the victim of the accident, but always seemed to be watching some one else falling in this manner.

When he went into the air he felt 'timid' and, if the air was still, he became drowsy. When this sensation came on he felt exactly as if he was 'sitting in an easy chair in front of a warm fire and falling off to sleep'. The 'fainting' came on suddenly, but the onset of the 'drowsiness' was gradual.

He sometimes had this feeling when he played lawn-tennis or billiards, or when he concentrated his attention on a book. We set him to play lawn-tennis under observation, and he was certainly unnaturally slow. When he wanted to take a backhand stroke, he could not bring his racquet across quickly enough to hit the ball. He complained that he found exactly the same difficulty in the air; he could not 'correct bumps', and was 'slow in adapting'.

Up to the time when he 'fainted' in the air he knew nothing of the abdominal sensations experienced by many persons when they descend in a lift. But he then began to be conscious of the 'feeling in the stomach', not only with any small displacement in the air, but also when going down in the lifts of the Tube Railway. He is certain that he never experienced this sensation of 'bumpiness' until February 1918. Since then he has never been free from it with the smallest drop or vertical bank. Moreover, when he had finished a spiral turn, the horizon continued to rush by for a long time afterwards in the direction in which he had been turning. This was another new experience.

When I saw him in August 1918 he was a well-built man of normal appearance, with no tremor of the hands or other signs of disease.

He walked a line and turned badly. He supported himself with difficulty on one leg and could not stand for more than 10 seconds on either foot. He failed entirely to balance the rod on the flat board with his eyes open or closed.

After ten turns in the chair he deviated strongly in the opposite direction to that in which he had been rotated, and did not reach the table at all. He staggered and fell into my arms as if drunk, and said he could not see anything distinctly enough to say in what direction the objects in the room seem to be moving.

5. *Comparison of the two reactions, 'Giddiness' and 'Fainting' in the Air.*

Any normal man can be made to suffer profoundly in the air if the rotatory alternations are sufficiently intense, and particularly if the head is held in some abnormal position. For example,

to look upwards at the top plane during a rapid spin is a certain means of inducing giddiness and nausea. In the same way, Major V. B. could provoke at will the preliminary symptoms of 'fainting' by executing evolutions which produced unusually intense rotatory stimuli.

Such reactions are not in themselves abnormal; but, in the examples I have quoted, they could be evoked with undue ease and were unusually violent. Sometimes the disturbance, due to changes in equilibrium, assumed the character of a true vertigo, accompanied by nausea and vomiting. In other cases it consisted of a withdrawal of consciousness, usually spoken of as 'fainting in the air'; this does not begin with a true vertigo, but with a feeling like that of passing under an anaesthetic. Surrounding objects grow distant, the 'horizon seems dark', and the actual loss of consciousness may be preceded by a drowsy state, in which it is impossible to act. The final event, as far as the pilot is concerned, depends on the stability of the machine. If it is of a type that passes out of a spin naturally on releasing the controls, the pilot may come to himself to find that he is flying far away from the point at which he lost consciousness; or he may have dropped several thousand feet. On the other hand, with many quick scout machines, which require an active effort before they cease to spin, the result is not uncommonly a more or less severe 'crash'.

Both the true vertigo and the loss of consciousness are the direct consequences of changes in equilibrium. What, then, are the underlying causes of this diversity of reaction? From an analysis of fifteen cases of 'giddiness' or 'fainting' in the air, where I was able to subject the pilot to exhaustive examination, I should like to put forward the following solution.

Out of ten pilots and observers who came under my care for giddiness and vomiting, all but one suffered in this way when they first went into the air; many of them succeeded in adapting themselves more or less successfully to the new conditions, until some factor arose which led to diminished control. They then regressed to the earlier reaction, and adaptation was no longer possible. It is interesting to notice that all nine patients had been unable to swing with pleasure in childhood, and many of them had been habitually sick in the train.[1] As they grew up, they gradually conquered this childish reaction; but, on being exposed to changes of equilibrium in the air, it returned. In most cases it was again brought under control, reappearing, however, with any cause which lowered the general resistance of the central nervous system. In the one case where the pilot had not suffered in the air during the early stages of his training, he

[1] It is interesting to notice the close association of rotatory vertigo and train sickness. For it is obvious that the latter is evoked from the visual apparatus, whilst the former is due to vestibular stimulation. The reaction is identical in spite of the diverse nature of the peripheral excitation. Another example of this order is the giddiness and nausea induced by rotating the walls of the room so that the victim, seated on a chair at rest, obtains an illusion of movement. One of the principal functions of the vestibular apparatus is to maintain the balance of the eyes; if this is disturbed, giddiness will follow although the semicircular canals have remained at rest.

began to vomit after an attack of influenza; this produced severe loss of weight and was followed by a constant feeling of fatigue. He had been, moreover, an unusually nervous child, and was not able to sleep without a light until he was sixteen years of age.

Giddiness and vomiting in the air are an expression of undue susceptibility to changes in equilibrium. This is usually constitutional; it may be so severe that it can never be corrected (No. 3), but in most cases adaptation is possible. The tendency to be giddy in a swing or to vomit in a train are overcome on the passage from childhood to adult life; in the same way, the reaction to disturbances of equilibrium may be controlled with the gradual acquisition of facility in the air. But any disturbance, physical or mental, associated with diminished general resistance in the central nervous system, will cause regression; the patient reverts to his original mode of reaction.

On the other hand, none of the five patients who 'fainted' in the air suffered from any discomfort on learning to fly; all enjoyed it from the first. Not one of them had ever been giddy in a swing or suffered in childhood from train-sickness. Evidently they were endowed with the power of controlling the effects produced by changes of equilibrium on the vestibular apparatus; vertigo, with its accompanying nausea, was absent. But when the impulses from the semicircular canals became too violent to be held in check they expended themselves by producing a withdrawal of consciousness. This begins with a narrowing of the field of attention, which may culminate in complete oblivion. Such a reaction may make its appearance in normal pilots, provided they push the rotatory stimuli up to unusual limits, as was the case with Major V. B. during his technical experiments. But under the conditions of normal flight fainting in the air at low altitudes is always evidence of diminished general resistance. Sensory impulses, which should be controlled, become capable of evoking an abnormal general reaction. This may be due to stress of war-flying (No. 10), to fear and anxiety (No. 11), to some gastro-intestinal condition (No. 8), to the after-effects of influenza (No. 9), and probably to a multitude of causes, which act in a similar manner.

But amongst the group of pilots who faint in the air, the natural resistance to vertigo is high; the impulses evoked by disturbances of equilibrium do not show themselves, therefore, in giddiness and nausea, but in a disturbance of consciousness.

This difference in reaction to changes of equilibrium in the air can be demonstrated by observations on the rotating chair. The effect produced upon those who were 'giddy' in the air was in sharp contrast to that produced in the group who had 'fainted'. Of the ten who had been 'giddy' and vomited, nine reacted excessively to rotation in the chair; they became more or less giddy, sweated, and suffered from nausea. The actual form assumed by the physiological response was not abnormal, but it induced an excessive general reaction with undue ease. In one instance only was this not the case; he had been shot down in aerial combat and his regression was assuming an almost pure psychopathic form.

On the other hand, of the five pilots who had 'fainted' in the air, three suffered from no discomfort of any kind after rotation in the chair; in two cases 'everything went misty'; and both patients complained that they felt exactly as they did in the air.

It would seem as if those who have a natural tendency to become giddy on rotation, react to disturbances of equilibrium with nausea and vomiting. Others can dominate the vertigenous aspect of the impulses from the semicircular canals; in them rotatory stimuli, if sufficiently severe, evoke the condition known as 'fainting'. How far the tendency of the reaction to assume this form depends on a predisposition to react to any severe shock by cardio-vascular disturbance, must be determined by future research. It may be found that even the 'fainting' induced by lack of oxygen is the same reaction of the central nervous system to stimuli of an entirely different order. My cases, however, are too few in number to afford an answer to this important question in applied physiology.

Wider experience may show that there are other forms of reaction which may occur in the air. Physiological responses are not inevitable and rigidly-defined manifestations. Such a case as No. 8 shows how closely related are the two reactions, 'fainting' and 'giddiness' in the air; for although the patient is classed under the first heading a violent dive on to a ground target induced nausea and many of the symptoms of 'giddiness'.

6. *Attacks of minor Epilepsy in the Air.*

In the early days of the war, before we were familiar with the pathology of 'fainting' in the air, some neurologists attributed the condition to minor epilepsy. But further experience has shown that this must be an excessively rare cause of pathological states in the air. I have met with one undoubted instance only; but the symptoms form such a striking contrast to the commoner form of flying disability, that the case seems to me worthy of record.

Case No. 12. Sergeant-Pilot, aged 24.

He joined the R.N.A.S. in September 1914, and went to Egypt in June 1915. Very shortly after his arrival, he was seen by the Medical Officer in an attack of minor epilepsy. He returned to England and was discharged on August 15, 1915, with this diagnosis.

He then learnt to fly at his own expense, and applied for a commission in the R.F.C.; he was, however, rejected on his previous history.

But in September 1916 he succeeded in joining without a Medical Board and, after passing through a theoretical course, went to a squadron as 2nd air mechanic. Here he rapidly learnt to fly, and gained his wings after about 20 hours in the air.

In March 1917 he went to France, and had his first and only severe accident in May of that year. He was flying a Sopwith two-seater. All he remembers is that, on rising 300 to 400 feet from the ground, he suddenly felt his arms and legs growing 'powerless' and he lost consciousness. He does not remember hitting the ground; but not more than a few seconds later he climbed out of his machine and helped his observer, who was hurt.

He had no conception of what had happened, and says he felt exactly as if he were a spectator, who had come to the rescue.

He did not fly for three weeks and then went to another squadron in France as a test pilot; there he remained for six months. He had no trouble in the air, but one evening, when walking with a friend, he suddenly became unconscious and fell to the ground.

In March 1918 he came to England and acted as ferry pilot; but he had many small attacks on the ground, and in September had a severe seizure in the street. He fell and became absolutely unconscious; he remembers walking on the pavement and then found himself in a tramway car with 'people fussing round' him.

He has been subject to these attacks ever since he was about 14 years of age. He 'suddenly loses count', becomes dazed, and then recovers to resume his work as if nothing had happened. When in the street, he has dropped things from his hands and walked on oblivious of his loss. He has never wetted himself or bitten his tongue.

In 1911 he had an attack whilst riding a motor bicycle. This led to a bad spill, and he severely injured three fingers of his left hand.

He enjoys flying intensely, and never feels better than when he is in the air. A long period of ground duty makes him depressed, and leads to a considerable increase in the number of the attacks. He has had one 'crash' only; but sometimes on long journeys, when acting as a ferry pilot, he has 'felt queer' in the air. He has always been fortunate 'to be high enough to come to myself all right, though I have lost height several times'.

One brother and one sister have similar attacks, and his father, who died of pneumonia, drank very heavily. The patient himself is a teetotaller.

He was a well-built rather nervous looking man. His heart was normal, and the pulse showed a perfect reaction to measured effort, returning with normal rhythm in one minute and a half.

His hands showed some irregular tremor, and his tongue was not steady. He could stand on either foot for 15 seconds on the first attempt, but could not balance the rod on the flat board, either with the eyes open or closed.

The pupils were of medium size but oscillated widely when his eyes were fixed on a distant point. The reflexes were normal, and there were no signs of gross disease in the nervous system.

This case differs from all those previously described in this chapter by the fact that the attacks occurred before the patient took up flying. Moreover, the majority happened on the ground and were associated with the usual manifestations of minor epilepsy. With care it should not be difficult to exclude even epileptics of this class from the Flying Services.

7. *Conclusions.*

Giddiness, vomiting, and fainting in the air may occur from many different causes apart from physical or chemical deficiencies in the atmosphere.

Candidates who show any signs of disease of the ear, nose or throat, are excluded from the flying branch of the Air Force. But the most careful examination cannot ensure that the pilot will not suffer from inequalities of tension in the middle ears on rapid changes in altitude. This is particularly liable to

occur if a cold or sore throat leads to partial or complete blocking of one or other Eustachian tube. This temporary change in the conditions of tension, external to the labyrinth, is a potent cause of giddiness, especially in scout pilots engaged in war-flying. It is characterized by the fact that it continues for a time on the ground after landing and is frequently associated with pain (Sydney Scott).

But there are many cases of giddiness and fainting in the air which bear no relation to abnormal conditions of those portions of the auditory apparatus external to the receptive nervous mechanism.

Any normal man can be made giddy during aerobatic evolutions, such as spinning, if he holds his head in certain unusual postures. We can bear with impunity certain violent disturbances of equilibrium if the stimulus is expended on certain parts of the vestibular apparatus, but not if it falls on other combinations of the semicircular canals. In the same way, provided a normal pilot is not unduly susceptible to giddiness, he can induce at any rate the preliminary stages of fainting in the air by pushing rotatory stimulation experimentally to abnormal limits.

But machines are so constructed, and pupils are taught to carry out aerobatic evolutions in such a manner, that the majority of normal men do not suffer from these symptoms in the air. There are, however, some in whom the physiological response is so violent that it can never be overcome, and they are always giddy and nauseated whenever there is any sudden or considerable change in equilibrium. Others suffer at first, but may overcome the reaction as they acquire facility in the air. Such persons are liable to regress under the influence of any condition, physical or mental, associated with diminished central control.

The majority of these patients could not swing with comfort in childhood and habitually suffered from train-sickness. When rotated on a chair the larger number were uncomfortable and suffered from nausea and sweating.

On the other hand, the pilots who came under my observation for 'fainting' in the air had all enjoyed flying from the first. They had experienced no discomfort in childhood, either when swinging or when travelling in the train. In two out of the five cases I was able to evoke that 'mistiness', which is one of the preliminary stages of fainting, by rotation in the chair; the others showed no abnormal reaction to this method of stimulation.

Epilepsy is one of the rarest causes of 'fainting' in the air. One definite case only has come under my observation during the later stages of the war, since the institution of a strict medical examination for admission into the Air Force. This is reported on p. 29. Differential diagnosis should not be difficult, for in this case, as might be expected, the larger number of attacks occurred on the ground under conditions that excluded any form of vertigo.

Chapter III. Sensations experienced by Normal Persons in Machines heavier than Air.

1. *Introduction.*

Balance in the air or on the ground depends primarily on the character and intensity of many diverse sensory impulses. Changes in the posture of the body as a whole affect the vestibular apparatus, the spacial aspects of vision, and the afferent mechanism of joints and muscles. If these various sense-organs function normally, the basis is given for those actions necessary to ensure stability, whether on the ground or in the air. Any external condition which produces an abnormal series of responses in any part of this complex sensory mechanism will lead to defective equilibrium. Giddiness, due to unregulated tension in the middle ear, and the disastrous effects of heterophoria are examples of such aberrant stimulation of normal sense-organs.

If want of balance were merely a matter of irregular external stimuli, or of some defect in the peripheral sense-organs, the question would be easy of solution. But I have been able to show that an abnormal reaction may be caused not only by faulty sensory impressions but by lack of what, for want of a better word, may be called 'higher control'. A man's 'muscular sense' may be perfect; and yet, when his eyes are closed, he may be unable to stand on one leg or to balance a rod on a flat board. His vestibular response, when rotated on a chair, may be normal, but the sensory impressions evoke nausea or the preliminary stages of fainting. Two factors must be considered in all observations on sensation, the character of the primary response and the nature of the final reaction.

Moreover, physiologists have long been familiar with the fact that a constant physical stimulus does not evoke in every case an identical physiological response. More mechanically-minded investigators are accustomed to assume that a strictly regulated physical stimulus must be followed by a directly proportionate functional response. On this hypothesis a body at a certain temperature should always produce an identical sensation of heat or cold; but this is notoriously not the case. A temperature of 30° C. may seem at one time hot, at another cold, according to whether the hand has been previously soaked in cold or in hot water.

Again, the impression produced by a physical stimulus, however carefully selected, is not of necessity simple, but is frequently extremely complex. It may evoke impulses which are incompatible with one another from the sensory point of view. Thus a temperature of 45° C. stimulates the heat-, the cold-, and the pain-spots; normally it produces a sensation of heat. If the mechanism for the reception of heat-stimuli is absent, 45° C. seems to be cold; if the part is insensitive to both heat and cold, pain alone follows the application of this temperature although it normally excites pleasant heat. In this case a physically simple stimulus evokes complex and incompatible

impulses, which must be sorted and integrated before they can form the underlying basis of a sensation.

Even then the struggle is not over. For it may happen that the mind is not at the moment attuned to accept a sensation of this kind; it is therefore suppressed, and does not enter the focus of consciousness. Under such circumstances some other group of sensory impressions may become dominant, to the exclusion of those more naturally anticipated. For example, we all know how certain forms of toothache are relieved by taking food. The physical cause of the pain is not influenced by the mechanical act of deglutition; but the neuralgia is inhibited for a time by the massive impulses poured into the central nervous system from the upper gastro-intestinal tract.

An identical stimulus can evoke in the same individual a varying response; what wonder that the action of the same physical forces may produce the most diverse effects upon different people. A good example of such differences, drawn from daily life, is the sensation produced by descent in a lift. Many people experience a peculiar 'sinking in the stomach' or 'feeling as if my stomach was being left behind' when moving downwards. Others have never been conscious of this sensation, unless the lift moves with a rapidity unusual in this country. Between these two extremes lie those who recognize this 'feeling' if the movement starts somewhat suddenly, but not under ordinary conditions. This sensation, like giddiness in the air, can be acquired. One young pilot knew nothing of any such 'feeling in the lift' until after an attack of influenza; the first time he travelled on the Tube Railway, on recovering from his illness, he noticed that the descent of the lift produced a peculiar effect he had never experienced before. When he returned to duty ten days later he found he had lost all confidence in the air and was 'gripping his controls tightly and tensely'.

Thus between the impact of the physical stimulus on the sense-organs and the final production of a sensation, lie innumerable possibilities of variation in the physiological and mental reactions. What wonder that the sensations induced by flying a machine heavier than air differ fundamentally in different persons, though the stresses and strains may be identical.

These individual differences start from the moment the machine leaves the ground. In some the uncomfortable bumping, caused by 'taxy-ing' across the aerodrome, gives place immediately to a feeling of profound security. If the passenger is strapped in with a well-fitting belt and his pilot is expert in correcting 'bumps', the machine seems to be the stable centre of the universe; it is the earth and sky that shift and move. A vertical bank produces no sensation beyond the feeling that the country with its roads, woods and houses is tilting in a peculiar and definite manner. Even during a flat spin it is the horizon that races round like the rim of a rotating bowl. An expert pilot talks in terms of a moving universe; he says, 'I came out to find the earth rushing up and so I pulled my stick back'; or 'My horizon was crooked, so I knew I was flying one wing down'.

In those who are fortunate enough to experience this stability from the first, it transcends any security obtainable on earth or sea. But many first-rate pilots have been frightened and unhappy on their first flight; they cannot believe that any one felt secure from the first moment he left the ground. With them confidence is acquired. But since it has been gained by practice it can also be destroyed by any condition which lowers bodily or mental vigour; and this is the case, not only with those who have adapted themselves to conditions in the air, but also with those in whom such confidence is innate.

Any experience which induces anxiety or fear may destroy the confidence of even the finest pilot. To be shot down in aerial combat, or to land in flames, is sufficient to upset the sense of security in any one, and may lead to subsequent want of adaptation to changes of equilibrium in the air. But should the concussion produced by the 'crash' abolish all memory of the events directly preceding the accident confidence may remain unimpaired. For this reason some who have passed through a terrifying experience can subsequently fly as well as ever. It has left no trace on the memory; the whole episode, including perhaps events of some hours before the ascent, has been entirely wiped out.

On the other hand, the sudden realization of danger may destroy all feeling of confidence on the spot (No. 11). The pilot not only feels himself insecure, but may become clumsy in his actions and suffer from abnormal sensations in the air. The anti-aircraft guns of the enemy produced more harm by undermining confidence in the air than by the actual destruction of machines; for when a pilot began to dream of 'Archies', he was near the end of his flying career at the front.

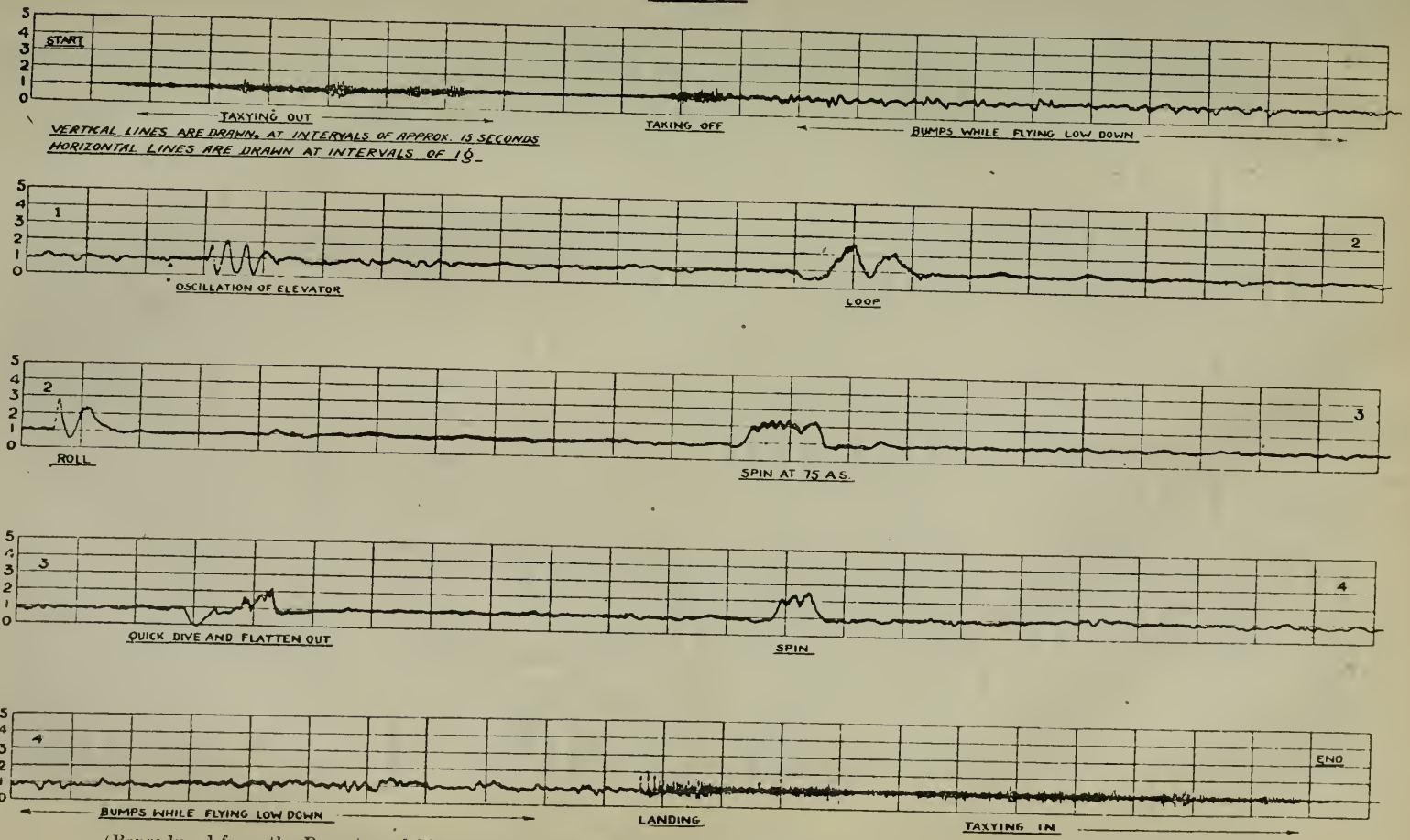
2. *Actual Experience during Aerobatic Evolutions.*

It is a matter of everyday experience that the same physical stimulus does not produce an identical effect on different human beings. But the physicist finds it hard to believe that the strong mechanical forces in action during aerial flight may lead to no conscious effect; and yet from a physiological point of view this might have been exactly anticipated. The more perfectly the passenger feels himself part of the machine, the more he will tend to translate changes of posture into some alteration in the position of surrounding objects. Stresses and strains disappear so long as there is perfect physiological adaptation to changes in equilibrium. In this way we gain a rapidity of action which would be impossible if every physical alteration entered consciousness and necessitated a corresponding action of the will. A good pilot does not fly by rule nor does he depend entirely on his instruments. When he wants to 'bank' he says, 'I just lean over and it comes,' exactly as when rounding a corner on a bicycle.

The following figure gives the actual forces to which the machine is exposed during various evolutions, as shown by means

VARIOUS MANŒUVRES ON A BRISTOL FIGHTER

29-3-18



(Reproduced from the Reports and Memoranda, No. 469, of the Advisory Committee for Aeronautics, by permission of the Controller, H.M. Stationery Office.)

of the accelerometer.[1] From this beautiful record it will be seen that a 'zoom' leads to a rapid drop to 0, followed by an irregular rise to 2 g,[2] just before the machine flattens out.

On looping, g first drops a little, then increases rapidly almost to 3, falls and rises again to about 2. A roll gives a similar but shorter rise, followed by a fall and a second flat-topped curve.

In spinning g runs up and oscillates round about 2, dropping quickly, when the machine is pulled out of the spin.

The actual sensations experienced by a passenger during these evolutions were determined independently by four medical observers. Colonel Birley, principal medical officer to the Headquarters of the R.A.F. in France, made a long series of experimental investigations from the back seat of a Bristol fighter. These form the basis of the inquiries summarized in this chapter. To Captain Rippon, medical officer to the 29th T.C.S. (the 'Medical Flight'), I am indebted for much personal experience of flight under varying conditions. Mr. Sydney Scott has also given me valuable information, especially with regard to giddiness and analogous sensations. Lastly, I have myself experienced, in an Avro, the effect of all these evolutions.

The whole matter was then discussed with a series of pilots, particularly with Major Bird, D.S.O., and his colleagues of the 'Medical Flight', who are accustomed to observe their own sensations and to listen to those of their pupils. To them my sincere thanks are due for their patience, and for the remarkable way in which they worked out these problems for themselves.

Most pilots, however, are not good witnesses in such an inquiry, unless their reactions are in some way aberrant. A normal pilot is so busy flying his machine, and is so instinctive in his reactions, that he has neither time nor attention to observe his own sensations. On the other hand, the four medical men who went up as passengers were not only trained observers, but were intent on discovering the effect produced by each evolution in turn.

In contrast to the evidence yielded by these normal individuals stands that of Captain H., a most skilful pilot, who returned from France, after six months' flying under war conditions, owing to nausea and vomiting. He was engaged on

[1] Report on the Measurement of acceleration on Aeroplanes in Flight, by G. F. C. Searle and W. Cullimore, June 1918.

[2] g is the symbol used for the acceleration per second of a body falling freely under gravity.

The weight is the mass multiplied by g.

Forces are proportional to the accelerations they produce on the same mass. Thus we may express the relative magnitudes of the forces acting on a body in terms of the accelerations these forces are producing.

The record (Fig. 1) gives the resultant force acting on any mass within the aeroplane in terms of the ratio of the acceleration that force can produce to the acceleration (g) which would be produced by gravity, acting normally. Thus, when the force registered is 1, it is exactly equal to that of gravity.

The supporting force of the seat, when sitting normally in a chair, is equal to g; seated in an aeroplane it is equal to g, multiplied by the number on the record, the value of which depends on the nature of the evolution being carried out. It is usually spoken of as 'one, two, or three g'. The excess or deficit above or below the value of g may be considered the measure of the abnormal physical forces acting on the body.

mechanical experiments in the air for the technical branch, and gave valuable evidence before the Committee on Accidents, especially in answer to my cross-examination.

Lastly, my thanks are due to Major V. B., another officer engaged in technical experiments, who was able to produce fainting in the air by excessive disturbances in equilibrium. He supplied me with many interesting details.

(a) '*Zooming*'. During this evolution the machine is dived steeply and then rises almost vertically in consequence of the great acceleration of momentum. Sometimes on quick-flying scouts the preliminary descent may be eliminated; the essential part of the 'zoom' is a steep climb. This throws an enormous strain on the machine and exposes the pilot to violent changes in stress.

All the medical observers, however, failed to notice any sensation during this manœuvre, and the three pilots of the 29th Training Squadron were of the same opinion; but they added that there was a sensation 'as if you were loose on your seat', when flattening out on the top of the 'zoom'.

On the other hand, Captain H. insisted that he felt his 'head being squashed into his body'; 'you feel you are being forced into your seat and it is impossible to move your legs though you can move your arms.' Here we find the first flat contradiction in testimony. Four highly-trained scientific observers and three pilots chosen for their perfect adaptation to conditions in the air, failed to perceive any sensation until the end of the manœuvre. On the other hand, a skilled pilot, with technical knowledge of a high order, who suffered from nausea in the air, was acutely conscious of the physical forces acting on his body during this evolution. In fact he said, 'If I were to lose this sensation, I should be worried, because then I might be putting forces on to the machine which would break it'.

Major V. B., the technical pilot who could make himself faint by carrying out certain experimental evolutions, was in complete agreement with the majority of the observers. He said that during a 'zoom' he 'felt nothing except the joy of doing it'.

Thus it is evident that what we call perfect adaptation to disturbances of equilibrium in the air is associated with control by the central nervous system of the various afferent impulses, evoked by the action of intense physical forces on the human body. Should they be permitted to rise into consciousness and cause sensations during normal flight, the pilot tends to suffer from giddiness and nausea when they reach any considerable intensity.

(b) *Looping.* None of the medical witnesses experienced any giddiness or definite sensations during an ordinary loop, and the three pilots of the 29th Training Squadron agreed with these observations. Colonel Birley noticed that, after the fourth or fifth consecutive loop, a sensation gradually came on of 'being loose in the seat'.

As might be expected, the account given by Captain H. again differs profoundly from that of the other observers. He feels that his head is being squashed into his body; as if he were

being forced into his seat. 'It is impossible to move your legs although you can move your arms freely.' This alternates with a feeling of 'decreased gravity'; 'it makes me feel as if my stomach was coming up. I sweat and may have nausea. I have put my head over the side but have never been sick.'

Major V. B.'s experiences are particularly interesting. He feels no sensation whatever during a perfect loop; but if he makes a short loop, a mist comes before his eyes like the early stage of going under an anaesthetic. If he makes five or six perfect loops consecutively he loses his horizontal and comes out to find he is flying wing down. 'You haven't the power to get her right unless you can get your head clear again. Something goes wrong after the third or fourth loop, which spoils their perfection.'

Here again we see the same difference in central control. In perfectly adapted persons simple looping produces no sensation, whilst Captain H. was sensible of the physical forces acting upon him throughout. These sensations came to Colonel Birley after a fifth or sixth consecutive loop only, and then in a mild degree. Major V. B. experienced nothing unless the loop was imperfectly performed, when he felt in a slight degree the preliminary sensations of fainting; a series of perfect loops disturbed his power of flying horizontally unless he made a definite corrective effort.

(c) *Spinning.* The effect produced by spinning in normal persons depends greatly on the position of the eyes and head. Pilots vary profoundly in the attitude they adopt; some keep their eyes on the instrument board and do not look outside the fusilage, others fix some point on the ground. Many pilots contend that if the eyes are thus directed throughout 'you remain conscious of your position in space, but if you look inside the fusilage you don't'. Both are safe methods and should not cause giddiness in normal persons.

Colonel Birley, who has made many observations to investigate this point, found that when he looked downwards during a spin he knew his position in space, but was conscious of forced movements. Thus, when spinning to the left (counter-clockwise), it would have been an effort to do anything to the right.

However well adapted a pilot may be to rotatory stimulation, he suffers from giddiness and frequently from nausea if he looks up at the top plane during a spin. Colonel Birley found that, on looking up, he 'lost himself entirely' and suffered from acute vertigo. 'I could not have done anything, and should have been incapable of all effort.' He was not, however, nauseated. Looking at the wing-tip is said by some to be even worse, and to be spun facing the tail is worst of all.

The account given by Captain H. is most instructive. During a spin he always looks straight forward at his instruments, and never lets his eyes wander outside the fusilage. On emerging from a spin he does not know where he is, but 'pulls out by rule'. He then finds that the 'horizon is crooked'. 'Something inside me would make me fly the machine one wing down.' During one set of experiments he looked up obliquely to the

left in order to count the turns by means of the sun, and was extremely uncomfortable. When he came out of the spin he was reading his instruments with great difficulty. 'I forced myself to do it; but it was a jolly big effort.' After coming out he stalled the machine badly and then dived; this was an unintentional manœuvre due to his state of mental confusion. He did not suffer from giddiness, but after it was all over felt sick. 'I felt bunged up and was unable to think clearly; I couldn't reason.' He is so familiar with this state that he has learnt by heart and repeats to himself exactly what he has to do, 'so that I mayn't have to think it out at the time'.

During these same experiments he carried out several more spins and nearly vomited. 'I felt something, under my lower jaw-bone, was being drawn upwards, and whenever I have felt this before I have always been sick. In this case I put my head over the side; but the drawing-up feeling below the tongue grew less and finally disappeared. I was not sick, though the feeling of nausea persisted for some time after I landed. I was very sick during the following night.'

Major V. B., a highly expert pilot, had the following experience whilst carrying out some experiments for the Technical Department. After an unsuccessful attempt to discover the smallest horizontal banked circle in which a Sopwith triplane could be spun, he got the machine into a turn at 3,000 feet. On starting the second turn 'the sky appeared to go grey'. 'A mist gradually arose like going under an anaesthetic,' and he 'fainted'. It was not an unpleasant sensation. When he came to himself, he was flying over a village about a mile away from the place of the experiment. The unconsciousness must have lasted about 20 seconds. During the first turn g reached 4·5, during the second 4·6. The turn was of about 140 feet at a speed of 114 miles an hour.

This pilot found experimentally that, whenever the acceleration (g) was pushed up to a high figure, he experienced the characteristic darkening of the sky which was preliminary to fainting. On another occasion he was looping and diving a D.H. 4 during a mock fight, when these preliminary sensations reappeared. He realized his danger and struggled against losing consciousness. First came a feeling of pressure in the head; then a mist gradually approached and spots rose before his eyes. He felt faint, chiefly at the bottom of the loop, and was quite conscious at the top. Then 'daylight' returned during the dive, and he came down about three minutes later feeling perfectly well. This preliminary sensation is distinctly pleasant, but is associated with inability to make an effort; 'it requires a definite struggle to right the machine.'

3. *The Human Element in Aeroplane Accidents.*

(a) *The Physiological Effects of disturbances of Equilibrium.* Normal human beings differ profoundly both in the intensity and in the character of their reactions to changes in equilibrium. Rotation in a chair, with the head erect and the eyes closed, is

usually followed by a tendency to deviate, and, on opening the eyes, surrounding objects seem to be moving in a direction opposed to that of the rotation. Thus, if a normal man has been turned clockwise, the apparent rotation of the room goes counter-clockwise, and the deviation takes a form determined by the position of the head during the turning. The average human being in perfect health rapidly overcomes these after-responses, and recovers his stability in a few seconds; moreover, he does not suffer from nausea or other abnormal sensations.

Such a patient as No. 3 (p. 19) was classed as abnormal, although he was in perfect physical health, because he invariably became giddy and was incapacitated by stimuli to which the majority of men could adapt themselves without difficulty. Such a classification is, however, purely arbitrary. Aeroplanes are so constructed that they can be flown by any healthy young man without producing vertigo or other disturbing symptoms; it would be possible to build 'freak' machines that required the talents and training of an acrobat to resist the giddying effect of their evolutions. Thus the criterion by which we judge whether an aviator is normal or abnormal depends ultimately upon whether he can adapt himself to those disturbances of equilibrium to which he is commonly exposed in the air.

Giddiness and forced movements are not uniformly proportional to the rotatory stimuli acting on the body. For exactly the same physical forces, which produce intense vertigo when looking upwards, may be without effect if the head is held in the usual position and the gaze is directed horizontally forwards. This can be shown by the following experiment. Whilst standing in the normal position, rotate the head rapidly from side to side; most persons experience little or no vertigo. But, if the eyes are directed to the ceiling and similar lateral movements are carried out, the majority of healthy people become giddy and rock on their feet. The physical forces are the same in both cases; but in the former they are exerted with the head in its usual posture, whilst in the latter the position is one to which we are not habitually accustomed. In the same way even a normal pilot can be made profoundly uncomfortable by looking upwards during a spin.

An even more insidious danger is the mental state which accompanies the physiological changes induced by rapid rotation. Colonel Birley found that, when he was spun counter-clockwise with his eyes fixed on a spot directly below him, it became difficult 'to do anything' to the right; if he looked upwards during the spin, he became incapable of all voluntary exertion. Sydney Scott came to the conclusion that some persons do not come out of a spin because they cannot realize that they must make a definite mental effort to pull the machine into a state of normal stability. Several pilots of experience bore out this suggestion. One of them said that in putting on the rudder to stop a spin he is reluctant to substitute 'a state of strain for a state of ease'; his tendency is to continue spinning too long. Another spoke of this condition as a 'sort of mental coasting'. Major V. B. was particularly explicit on this point; he has been

throughout so conscious of the danger of this pleasant mental state that, as soon as he feels it beginning, he cuts short the manœuvre.

So long as the machine is one which will come out of a spin when the controls are released, the pilot may become unconscious and yet no accident happen. But if a definite act is required to terminate the rotation, as on a Camel, it is obvious that the machine may spin into the ground because the pilot has been rendered incapable of the necessary voluntary effort. The more rapid the turns the more likely is it that this condition will be induced; and it is not improbably responsible for some of the accidents on very delicate scout machines such as Camels. Where, however, the pilot is seen to fall into a spin, to come out again and to spin into the ground in the opposite direction, it is possible that forced movements are responsible for the reversal of rotation after the first recovery.

(b) *Regression.* Flying, like the ability to play games, is definitely acquired and maintained by practice, and the measure we apply to all such human activities is the extent of functional efficiency. Now all action is based upon reflexes, which are controlled by the activity of higher centres; these in turn are dominated from above, and the active life of the central nervous system is comprised in a hierarchy of functions. Finally, consciousness stands as commander-in-chief over a vast number of subordinate activities, each of which is itself in authority over some more lowly mechanism.

To refer everything to the central authority would be a slow and laborious method of action; power is therefore delegated to the various departments to act without reference to the central administration. The lines of action are, however, laid down from above; we acquire a new aptitude by conscious effort excited through lower motor and sensory mechanisms. When learning to play the piano the fingers are laid consciously on each key and a complicated apparatus is thrown into action which strikes the note. Soon, with practice, the fingers move automatically and consciousness is occupied in reading the musical symbols on the printed page. Finally, with increased facility even this becomes almost automatic; the expert musician scarcely sees the page, for the nature of the musical phrase suggests to him the sequence of the accompanying harmonies.

First, the mechanical apparatus must function perfectly; the strings must be in tune and the levers which move the hammers perfectly adjusted. The fingers must learn to strike the right keys and the two hands be co-ordinated and controlled. This after long practice becomes automatic. At the same time there must be perfect comprehension of the musical notation and strict combination of mind and hand. Finally, in the supreme state of functional aptitude, the printed page suggests a musical thought which is automatically manifested as a series of sounds.

In the same way the aviator slowly acquires increasing facility in manipulating a complicated apparatus. At first he laboriously flies by rule and has to memorize the steps by which each evolution is induced. As he becomes more expert he has but to desire

some movement and it occurs; for a good pilot flies automatically and not by formula. He corrects, and may almost be said to anticipate, 'bumps' by instinct.

This power over the machine has been gained by conscious effort, during which a series of functional adaptations become engulfed in the automatic activities of the central nervous system, as soon as they are acquired. Movements laboriously learnt become unconscious reactions. But this supreme control can only be maintained by constant exercise and perfect physiological efficiency. Any influence which tends to diminish the power of concentration or to disturb the acquired mastery over sensory and motor impulses will lower ability to fly. The pilot becomes aware that he has lost his certainty in landing or is inclined to make flat turns. He does not know why he is no longer master of his actions, and complains 'I do everything that used to make me land perfectly, but it only comes off once in three or four times'. Like a golfer, he is 'off his game'. He does not know what is wrong because, when perfect facility has been acquired, the act has become automatic.

It is a well-known physiological law that when the control by a higher centre over some lower activity is diminished the character of the reaction tends to take on a more primitive form. The lower centres released from control are free to exercise their activities unchecked. For example, in hemiplegia the paralysed arm is frequently in a condition of great rigidity. This is due to the loss of that control usually exercised by the cortex of the brain over the lower motor centres. In the same way removal of the dominant influence of the sensory cortex on the afferent activities of the optic thalamus causes the paralysed half of the body to become over-sensitive to all painful or pleasurable stimulation. This phenomenon is usually spoken of as the 'release' of lower centres.

Here one crude structural centre of later development dominates another with more primitive reactions. But a similar law governs the inter-relation of a series of functions, each of which has been in turn acquired by practice and conscious effort. On the piano the fingers must first be taught to strike the right keys; then the two hands must work in a co-ordinate manner. As each new facility is gained it becomes automatic and disappears from the focus of consciousness. But with loss of control, movements once performed without thought require an effort of attention, and both mind and hand make apparently inexplicable mistakes. If the error takes the form of some fault previously overcome by practice we speak of 'regression'. The sufferer has fallen back on some previous method of reaction.

This unexpected return to some previous habit is one of the commonest human errors in all mechanical activities. Innumerable instances can be gathered from games and from daily life. A man who has driven a motor-car with the levers to the left, and then becomes habituated to the more ordinary form with a right-hand brake, may find in an emergency that he is groping to the left. A golf-player who is 'off his game' finds that he has fallen back to some long-conquered fault. This might be called

mechanical regression; some action, which has been acquired in perfection and has become automatic, may be disturbed by failure of control and is consequently carried out in an inferior manner.

But regression may be manifested not only in a motor act, but also on the sensory side. A tendency to giddiness in the air may be overcome with the acquisition of aptitude to fly. The physical stresses and strains to which the pilot is exposed remain the same, but the afferent impulses they cause are integrated and controlled. If, however, the general physiological resistance of the nervous system is lowered, or the power of mental concentration diminished, sensations of unusual intensity may be aroused accompanied by giddiness and nausea. A pilot may regress to the form of reaction which troubled him when he first went into the air.

The war has furnished frequent examples of the mental aspects of regression. A soldier is sent home suffering from the stress of fighting; he complains of horrible dreams, which take the most diverse and individual forms. Night after night he wakes in fear. But after suitable treatment these terrors cease and his dreams are occupied with the petty worries of the day. Suddenly all the old horrors return in consequence of some great sorrow or anxiety, such as the death of his wife or illness of a child. He has regressed to a previous psychical reaction in consequence of diminished mental control.

Not uncommonly all aspects of regression are manifested in the same patient. A pilot finds he is no longer flying with certainty; he is obliged to think of what he is doing instead of carrying out the manœuvre automatically. This frightens him, and the fear causes widespread regression. He may become giddy or faint in the air, and will probably 'crash' unexpectedly. He complains of frequent nightmares; these may be concerned with horrible events, previously forgotten, which occurred when he served in the trenches. Or he may be haunted by visions of a machine falling in flames, the reappearance in symbolic form of an old fear on first flying over the lines.

Thus regression may lead to the loss of mechanical aptitude, to an abnormal reaction due to the uncontrolled activity of sensory impulses, or to the reappearance of some less efficient form of mental activity. It is of profound theoretical interest, and probably explains certain apparently incomprehensible accidents in the air.

General Summary.

1. Conscious stability and comfort in the air depend primarily on the normal response of three groups of sense-organs. These are the vestibular apparatus, the eyes, including the eye muscles, and the proprio-ceptive system with its endings in muscles, tendons, and joints.

But of all the afferent impulses evoked by the impact of physical forces on these various mechanisms, those underlying the projected aspects of sensation are alone of significance in the

present inquiry. We are interested in those impressions which lead to recognition of the position of the body in space.

2. Defective responses from any one of these afferent end-organs will disturb the sense of equilibrium in the air, and may lead to actions that affect the stability of the machine.

3. No candidate for service in the R.A.F. is accepted who shows gross abnormality of any one of these primary organs of sensation.

But in the course of flying a machine heavier than air, an otherwise healthy man may suffer from disorders of vestibular and visual sensibility due to temporary causes. He may not be able to regulate the tension in the middle ear with sufficient ease during a rapid descent and consequently becomes giddy; or his eye muscles may no longer function strictly in unison, and he may develop heterophoria with its resultant lack of visual orientation.

4. The tests at present in use by the Examining Boards for estimating the sense of balance may reveal the existence of some abnormal functional state, but are not otherwise an indication of ability to fly.

5. Standing on one foot with the eyes closed, walking a line heel to toe, and balancing a rod on a flat board, are not tests for 'Muscle Sense' or 'Vestibular Stability', in the class of young men from whom the pilots and candidates of the R.A.F. are drawn. Failure to pass these tests, however, indicates some want of afferent or efferent central control.

6. The presence of Tremor, especially of the hands, is of great importance; it points to some distinct defect in static control, and is definite evidence of disordered function.

7. In some men, otherwise normal, rotatory stimuli produce a more powerful reaction than in the majority of their fellows. They become giddy easily. As children they could not swing with pleasure, and some of them were habitually sick in the train. Such persons are not suffering from a pathological condition; their disability arises from the fact that sensory impulses from the semicircular canals are not checked and controlled to the same extent as in the majority of healthy individuals. Consequently, when exposed to disturbances of equilibrium to which a normal man would adapt himself unconsciously, they suffer from discomfort, become giddy, and may even vomit in the air.

8. Many who were giddy when first exposed to aerobatic evolutions, succeed in conquering this disability. They learn to fly with ease, and the acquisition of this new facility is associated with control of the primary afferent impulses from the auditory and visual apparatus.

Any condition which produces diminished control by the highest faculties over the activity of lower centres, is liable to lead to regression to the earlier mode of reaction.

9. All healthy men can be affected if the intensity of the rotatory stimulus is pushed up to a sufficiently high degree. This may occur either from the fact that the head is held in some unusual position, as for example when looking upwards during spinning, or the actual rotation may be mechanically increased in rapidity.

In some cases the reaction to such excessive stimulation takes the form of giddiness with or without nausea; in others it is associated with that withdrawal of consciousness known as 'fainting'. When a man is made giddy he is in a state of confusion with regard to his relations in space. In the preliminary stages of 'fainting' his horizon is restricted and the world around disappears. Both states, pushed to the limits of endurance, end in unconsciousness.

10. Complete adaptation to disturbances of equilibrium in the air is associated with automatic control of the afferent and efferent activities of lower levels of the central nervous system. A perfect pilot desires that his machine shall behave in a certain manner, and the evolution occurs, exactly as an instrument in the hands of a skilled musician emits the appropriate sounds as soon as he becomes conscious of some harmonious phrase.

11. This acquired facility can be disturbed by any condition which leads to diminished control. Just as a golfer can be 'put off his game' by some physiological or mental state, so the aviator may lose his capacity to fly in consequence of conditions that vary so widely as a gastro-intestinal attack or domestic anxiety. Exhaustion, insomnia, the distress of war flying, anxiety or fear, can all lead to defective afferent and efferent control. Efficient automatic response is no longer possible, and the pilot begins to fly badly and to make bad landings.

12. But this loss of control over the activity of lower levels may be manifested not only in bad management of the machine, but in some dangerous reaction such as 'giddiness' or 'fainting' in the air.

13. Should this abnormal reaction assume the form of giddiness and nausea, it will be found in most cases that the patient has suffered from some discomfort when he first went into the air. Inquiry will usually reveal that he was unable to swing with pleasure as a child, and that he tended to be sick when travelling by train.

On the other hand, all the five pilots who came under my care for 'fainting', enjoyed their first flight and could swing with pleasure.

In the first group rotatory impulses, when released from control, manifested their influence in giddiness, usually accompanied by nausea. Amongst those who 'fainted' in the air the resistance to vertigenous impressions was high and no excessive giddiness resulted; but they induced the effects of shock with undue facility.

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A Contribution to the Study of Chronicity in Dysentery Carriers

Approved for publication by the Medical Research Committee, October 18, 1918.

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INTRODUCTION

The Committee are indebted to the War Office for permission to publish this Report by Captain W. Fletcher, R.A.M.C., and Dr. Doris Mackinnon, upon the results of their investigation of 935 dysentery convalescents and 847 patients convalescent from other diseases, admitted to the University War Hospital, Southampton, between May 1917 and May 1918. This work, to which the Committee have been able to give some assistance, has included careful inquiries into the past history of each case, with laborious and exceptionally thorough laboratory investigations, and it has thrown fresh light upon some sides of dysentery which have hitherto received relatively little attention.

The principal object of the authors was to study the chronicity of both bacillary and amoebic dysentery and to ascertain the relative frequency and the degree of persistence of the carrier condition in each variety. The conclusions at which they arrived have led them to make a series of recommendations at the end of the Report upon the disposal of these cases and the undesirability of the retention of persistent carriers, or of chronic and relapsing cases, upon the active strength of the Army. Although the termination of hostilities and the rapid demobilization of the forces has, of necessity, largely modified the pre-existing regulations governing the disposal of dysentery convalescents and carriers, the work of Captain Fletcher and Dr. Mackinnon, detailed in this Report, was of great assistance to the War Office Committee on Dysentery in their framing of the recommendations to which effect has recently been given in a revised Army Council Instruction dealing with the subject.

The authors' accurate observations of the intermittency of the carrier condition, especially in Flexner infections, of the commonly tropical or sub-tropical origin of Shiga infections and their greater tendency to become chronic and to affect the general health, as well as of other points, may be expected to have permanent value in the study of the dysenteric infections.

Medical Research Committee,
15, Buckingham Street,
Strand,
London, W.C. 2.

A CONTRIBUTION TO THE STUDY OF CHRONICITY IN DYSENTERY CARRIERS

BY

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I. Introduction.

From the middle of May 1917 we made it our practice at this hospital to question as to their foreign travel and previous attacks of diarrhoea and dysentery all patients found by us to be carriers of *Bacillus dysenteriae* (Flexner and Shiga), or of *Entamoeba histolytica* (Schaudinn). With very few exceptions the men we examined had been invalided from France; we began taking 'histories', chiefly with the intention of collecting further data concerning the prevalence of infections among persons who have never been in the tropics or the Near East.[1]

At first the histories were not taken down in much detail; we satisfied ourselves by asking whether the man had ever been in the tropics, whether he had ever had dysentery before, and if so, when and where; but we soon found that, while many of the cases were recovering from their first attack of dysentery, and

[1] The evidence on this point, in connexion with *E. histolytica* infections, is treated by one of us (D. L. M.) in a separate paper.—'Notes on the Intestinal Protozoal Infections of 1,680 men examined at the University War Hospital, Southampton,' *Lancet*, Sept. 21, 1918, p. 386.

had presumably acquired their infections in France, a considerable percentage had suffered from dysentery for a number of years. It occurred to us that it would be interesting to get some evidence from these men on the question of chronicity. We accordingly made closer inquiry into the origin of the attacks, and traced, as carefully as we could from the men's statements, their movements, and the history of their dysentery from the date of the first attack. As our questions grew more searching and we collected a reasonably large number of histories, the fact emerged that the bulk of the cases with long records of dysentery had first suffered from it in some tropical or sub-tropical region, either before or during the present war.

It is widely recognized that an infection with *E. histolytica*, once established, is often of very long duration. Recently several attempts have been made to get exact information on the point. Wenyon and O'Connor (*Human Intestinal Protozoa in the Near East*, 1917) give authentic instances of three men who had suffered from dysentery for five or six years, and were passing *E. histolytica* cysts at the end of that time; Dobell and Stevenson[1] quote the cases of three men who had suffered from amoebic dysentery, at intervals, for periods of 16, 28, and 34 years respectively.[2] Wenyon and O'Connor, in the above work, go so far as to say that, 'so far as we can judge, it (the infection) may last for the rest of life'.

While it is everywhere admitted that these protozoal invasions of the intestine are very apt to become chronic, it does not appear to be generally known that, as we shall show later, the infections of bacillary dysentery, also, have a great tendency to become chronic.

Among the men examined by us, some of the older men, and the old regular soldiers more particularly, gave records of dysentery dating back to service in India in 1904, 1905, and 1906; and one had his first attack of dysentery during the Boer War, 1900; but for the great part we were, of course, dealing with quite young soldiers, and men who, as a class, had not had much opportunity for foreign travel. Except for the colonials, very few of them had been out of England before they left it with the army during the present war. The Gallipoli Expedition of 1915 was therefore the starting-point of most of the long infections among them; Egypt and Salonica added their quota then and in the following years; Mesopotamia, East and West Africa, and Palestine were responsible for comparatively few of the infections in men examined at this hospital of whom we have the records.

It is, of course, impossible in many cases to link the first with the subsequent attacks, and, especially where long 'healthy' intervals have elapsed, it would be rash to do so: in the conditions of active service there is ample opportunity for reinfec-

[1] 'A note on the Duration of Infections with *Entamoeba histolytica*' (1918), *Trans. Soc. Trop. Med. and Hyg.* xi. 168.

[2] On dysentery relapses see also Waddell, Banks, Watson, and Redman King (1917), *Lancet*, July 21, p. 73, and Glynn, Berridge, Foley, Price, and Robinson (1918), Medical Research Committee's Special Report Series, No. 7.

tion, not once but many times. It seems probable, however, that where men have been much troubled with diarrhoea and have passed blood from time to time in the months between the acuter manifestations of their dysentery, they have never really been cleared from the original infection. Such men are liable to frequent breakdown through a recurrence of the old trouble, and their condition may be described as 'chronic'.

If we, somewhat arbitrarily, use the term 'chronic' to mean that a man has suffered in this way for a period of at least a year before he was examined at this hospital, then we find that 88, out of a total of 229 cases whose histories were taken, come under this category. The majority of the 88 had suffered for much longer than a year. Thirty had had dysentery at intervals since the beginning of 1916, 37 since 1915, 4 since 1914, 5 since 1913, 2 since 1912, 1 since 1911, 2 since 1909, 2 since 1906, 1 since 1905, and 4 since 1904.

The impression one receives is that the work put into 'curing' these chronic cases sufficiently for their return to active service with the army is largely wasted effort. With care, rest, and dieting most of them recover some degree of health, put on flesh, and are fit to perform light duties without ill effect. They seem stronger than they are. To judge simply by their appearance when they leave hospital, and to pass them as fit for active service in the field is, we believe, to ensure the speedy return to hospital, with dysentery, of nine such cases out of ten. The intestinal ulceration of a chronic dysentery patient is, we may assume, incompletely healed, and perhaps unhealable: heavy physical strain, exposure to chills, rough or unsuitable food, soon undo what good has been effected by hospital regimen, and the expenditure of time, money, and labour over their frequent transfers, examinations, treatments, convalescences, and discharges is no small consideration.

The effect on the men themselves of these repeated breakdowns is often pitiable. They become exceedingly despondent and hopeless of cure. Several of the older men, who had suffered with dysentery in civilian life, explained that, 'given a chance to diet' themselves, they used to be able to keep the dysentery under. 'I'm all right, and then directly I get back to bully-beef and Maconochie I'm bad again,' was a common statement.

We think that, in passing dysenterics for return to service, medical officers do not pay sufficient attention to the men's past records. Unless they make inquiry into the question of previous attacks they can have no real measure of the extent of the calamity that may have befallen a man, or of judging whether he is at all likely to be able to serve without further relapse.

We should like to recommend that men with records of several relapses of dysentery during the two years before their examination by a Medical Board (more especially where the acute attacks have been linked up by frequent diarrhoea) should, if they are not 'carriers', either be discharged from the army when their dysentery has subsided, or should at least be placed in a lower category in the army. We are convinced that such men are lost as active soldiers.

It is more difficult to suggest what should be done with those chronic cases which have been in hospital for long periods, and yet show no substantial improvement. On these men everything has been tried that can be tried in the way of diet and treatment; emetine in various forms has proved unavailing; they continue to pass blood and mucus, and some of them still pass pathogenic organisms. On considering their records we are struck by the fact that so much time, trouble, and money is spent in transferring them from one hospital to another. Clearly such men cannot be returned, as they are, into the civil population, and there should, we think, be some more effective means of retaining, at a permanent depot, chronic dysenterics of this type, whether they be found 'carriers' or not.

During the course of the examination of 1,782 convalescents, we recorded the histories of nearly all those who were found to be carriers of dysentery bacilli or of *E. histolytica*. In this way we collected records of 74 bacillary carriers and of 122 carriers of *E. histolytica*. In addition, we took the histories of 42 dysentery convalescents, in whose faeces no pathogenic organisms were found while they were in this hospital, because we thought it possible that, amongst these 'negative' patients, the percentage of chronic cases would be a good deal lower than among the carriers: but, as a matter of fact, and making allowance for the much smaller number of 'negatives' written up, the proportion of chronics, in both groups, was closely similar.

The records were taken down from the patients' own statements, supplemented with information obtained from their Field Medical Cards and the reports of laboratory examinations made in France and elsewhere.

We here deal with the evidence of chronic dysentery which we have obtained in the three groups of men concerning whom we have made inquiries.

(I) Bacillary carriers.
(II) Carriers of *E. histolytica*.
(III) Dysentery convalescents in whose excreta no pathogenic organisms were found while they were here.

II. Group I.

1. *Carriers of B. dysenteriae.*

General Considerations.—We have endeavoured to determine to what extent chronic dysentery is due to the presence of dysentery bacilli, and whether persistent bacillary carriers suffer from repeated attacks of dysentery.

While it is everywhere admitted that the carrier plays an important part in the dissemination of bacillary dysentery, we do not think it is generally recognized that such infections are very prone to be persistent.

It is necessary at the outset to define what we mean by a *Persistent Carrier*. We have included in this class any patient who remained a carrier of dysentery bacilli longer than three months after the beginning of his illness.

When classified thus, more than 20 per cent. of the convalescents who excreted Flexner's bacillus, and all those from whom Shiga's bacillus was isolated, were found to be persistent carriers.

As several workers have expressed doubts as to the value of examining the excreta of dysentery convalescents for the purpose of detecting bacillary carriers, it may be useful to give figures of the results obtained in this laboratory for the twelve months ending May 1918. During that period 935 convalescents from dysentery (including diarrhoea, enteritis, and colitis) have been examined, and 847 convalescents from other diseases, such as enteric group infections and trench fever. Nine carriers of Flexner's bacillus were found in the latter group, while among the 935 dysentery convalescents, in the first group, there were 52 Flexner and 13 Shiga carriers; i.e. 65 or 6·95 per cent. of dysentery carriers. Thirteen of the Flexner and all the Shiga carriers, i.e. 26 or 2·78 per cent., were persistent carriers.

The excretion of Flexner's bacillus is so apt to be intermittent that it is more than likely that several intermittent carriers were overlooked, and that, in reality, considerably more than 20 per cent. of the carriers of this bacillus were of the persistent type. In most cases, Flexner's bacilli are found at rare intervals; the intervals frequently last for four or five weeks, and may be much longer, so that unless the patients, from whom they have been isolated, are examined daily and over long periods, they will probably be missed.

It is our practice here, when dysentery bacilli are found in a patient's stools, to examine specimens daily until the results have been negative for four weeks, and then to transfer the patient to the dysentery depot at Barton. If he remain a carrier, in spite of treatment, he is sent to Addington Park War Hospital, instead of to Barton, with a view to further treatment and disposal. Working on these lines, it has been found necessary to send 7 out of 13 persistent Flexner carriers to Addington Park, and no fewer than 10 out of 13 Shiga carriers, because they showed no signs of becoming clear of infection.

Judged from the point of view of physical efficiency the Flexner carrier and the Shiga carrier occupy very different positions.

The average Flexner carrier is in good health; his stools are formed and free from blood and mucus if his intestine has not been damaged by inflammation due to amoebae or to some other cause, and he is fit to carry on his work unless he is subjected to very adverse conditions of feeding, temperature, or labour, which may induce attacks of diarrhoea.

The Shiga carrier, on the other hand, is generally an invalid; his stools usually contain blood and mucus, and he has frequent attacks of diarrhoea; but this is not all, for in addition to his bodily ailments he often becomes a mental wreck. The weakening effect of the constant diarrhoea, the straining and tenesmus, the dragging sensation in the abdomen, the concentration of the attention upon the presence or absence of blood and slime in the stools, and the frequent disappointment due to repeated

relapses, tell upon the patient's mind and reduce his mental state to one of misery and dejection.

We have lately had men brought to the laboratory in batches for vaccine treatment, and we have seen that it is possible to pick out the Shiga patients from amongst the Flexner carriers by the melancholy gloom upon their faces. This we have seen also in patients who have suffered from amoebic dysentery, but never in Flexner carriers, and we feel convinced that few, if any, persistent carriers of Shiga's bacillus will ever again be fit to lead the active life of a soldier.

As there is so wide a difference between the two groups of carriers of the Shiga and of the Flexner types of dysentery bacilli, we have decided to consider them separately.

2. *Carriers of B. dysenteriae, Shiga.*

Infections with Shiga's bacillus, as seen among the convalescent patients admitted to the wards of this hospital, are so different, clinically, from other bacillary invasions of the intestinal tract that, as remarked above, it is necessary to consider them as a class by themselves.

These infections have four salient features. First, the state of illness, debility, and mental depression to which the carrier is reduced by chronic inflammation of the intestine and the frequent passage of blood and mucus.

Second, the chronicity of the infection, which may endure for months, or even years, and may resist all attempts to eradicate it.

Third, the liability to repeated relapses whenever the carrier ceases to lead the quiet life of a semi-invalid, and attempts work of an arduous nature, or eats indigestible food.

Fourth, the evidence that in the majority of cases the disease was contracted in the East.[1]

Most people on reading the above statement would say at once, 'These are the features of amoebic dysentery'; and indeed the history of chronic Shiga infections is almost identical with that of amoebic dysentery; but there is one important difference. healthy carriers of *Entamoeba histolytica* are very common, but such carriers of *B. dysenteriae* (Shiga), though they exist,[2] are remarkably rare. The resemblance of these men's symptoms to amoebic dysentery, coupled with the fact that most of them had come from the East, at once suggested that the presence of dysentery bacilli might be secondary to protozoal disease, and with this in view their excreta were searched diligently, on many occasions; but these examinations, so far from revealing an undue proportion of carriers of *E. histolytica*, showed that only one of them was infected, though more than 13 per cent. of all the convalescent dysentery patients admitted to this hospital have been found to harbour the cysts of this protozoon.

Infections with Shiga's bacillus have not been common among

[1] See Douglas, Colebrook, and Morgan: Medical Research Committee's Special Report Series, No. 6, p. 54.

[2] See Rajchman and Western: Medical Research Committe 's Special Report Series, No. 5, p. 11.

the convalescent patients admitted, and the organism has been isolated from only 13 patients. All these 13 men looked ill, and had lost weight, but, taken together as a group, perhaps the most noticeable thing about them was their condition of mental depression.

One of the patients was suffering from subacute dysentery. All the rest were 'below par', and all of them were passing mucus, and sometimes blood, in their stools. It may be argued that such cases as these should not be included in the category of carriers, but, excluding the subacute case, though unfit to do heavy manual labour they were by no means bedridden, and, in civil life, they would doubtless have been employed in various occupations not requiring great physical exertion. They would have associated with their fellow men, and would have moved amongst them, unsuspected sources of danger to the public; so that, on practical grounds, they should be classified as carriers.

The chief characteristic of the infections with Shiga's bacillus seen in this hospital has been their chronicity. Ten of the 13 men from whose excreta the bacillus was isolated continued to be carriers in spite of treatment, and were transferred to Addington Park War Hospital for disposal. It is difficult to say when, exactly, these men contracted the disease, because most of them had suffered from dysentery on more than one occasion, so that in calculating the duration of the infection we have counted the time that elapsed since the commencement of the last attack, which, of course, is underestimating its length in at least some of the cases. Three of the men (W. B., D., and H.) were transferred as chronic carriers about five months after the commencement of their illness, and 5 (L., G., Sh., Gr., and P.) had been ill for a year or more when they were transferred to Addington Park. Three of the men had never had dysentery before, but the other 10 gave a history of previous attacks, subsequent to which they had been liable to occasional diarrhoea if they were not careful in their diet, caught cold, or over-exerted themselves.

Only 25 per cent. of the convalescents who have been examined in this hospital, during the last twelve months, have served in any other theatre of war than France; this probably accounts for the comparatively small number of Shiga carriers met with, because the majority of infections with this bacillus are contracted in the East. In only 2 of the 13 cases (J. B. and W. B.) could it be proved that infection had taken place in France; all the others had come either direct from the East, or had suffered from previous attacks of dysentery while they were there. In 5 of the cases the disease was a legacy from the Dardanelles campaign.

Very little immunity against the infection, as indicated by a measurement of the agglutinins present, was developed in the blood of these 13 patients. The serum of each patient was tested with an emulsion of the dysentery bacilli isolated from his excreta and also with the Oxford 'standard emulsions'.

As shown in the table below, the serum of none of these men contained a large quantity of agglutinins; 8 of them did not

agglutinate cultures of their own bacilli in dilutions of 1 in 20, and H.'s serum was the only one which did so in a higher dilution than 1 in 80.

TABLE SHOWING AGGLUTINATIONS OF SHIGA STRAINS ISOLATED.

Name.	*Shiga agglutinin units in 1 c.cm. of serum.*	*Agglutinations of patient's culture with patient's serum.*
L.	20	0
G.	10	1/20
Sh.	10	0
Gr.	0	0
P.	10	0
D.	20	1/80
W. B.	4	0
H.	not done	1/400
C.	10	0
J. B.	20	1/40
St.	0	0
W.	5	0
Wr.	not done	not done

The several strains of dysentery bacilli isolated were true to type. They all produced acid in glucose and in milk, the latter becoming alkaline from the fifth to the eleventh day after inoculation. They were all tested with an immune serum, D 10. from the Lister Institute, the stated titre of which was 1/1000, and each of the 13 strains was agglutinated by a dilution of 1/3200.

As is shown in the table below. the excreta of these 12 men were examined repeatedly, and Shiga's bacillus was found in more than a third of the examinations. The infections were not characterized by long intervals during which dysentery bacilli could not be found in the excreta—the longest 'negative' interval was 13 days, in the case of J. B.

TABLE SHOWING NUMBER OF SPECIMENS EXAMINED AND THE NUMBER OF TIMES SHIGA'S BACILLUS WAS ISOLATED.

Name.	*Number of specimens examined.*	*Number of times B. dysenteriae, Shiga, isolated.*
J. B.	93	23
W. B.	80	32
C.	12	4
D.	51	16
G.	32	32
Gr.	11	5
H.	61	35
L.	30	19
P.	22	10
St.	31	3
Sh.	30	25
W.	10	2
Wr.	6	1
	Total 469	Total 207

In order to illustrate what has been said with reference to persistent infections with Shiga's bacillus, the following 5 cases are given as examples:

Case 2812, *Pte. L.*—This man was first taken ill during September 1916 in Salonica, and he has been in hospital ever since; his stools have never been free from blood and mucus, and 89 weeks after the beginning of his illness he is still a carrier. In October 1916 he was sent to hospital in Malta; in March 1917 he was transferred to England, where he was a patient first at Stockport and then at the Hope Hospital, Manchester. From Manchester he was sent to the dysentery depot at Barton on Feb. 22, 1918, and, on Mar. 26, 1918, he was transferred to this hospital as a case of 'colitis'. The patient stated that Shiga's bacillus was isolated at Malta, and Major Sellers has kindly informed me that, in Manchester, he was found to be a carrier of *E. histolytica* and was treated with E. B. I. pills. He has been examined 30 times in this laboratory and *B. dysenteriae* (Shiga) has been isolated on 19 occasions. Ten examinations for protozoa have been made with negative results. His faeces contained blood and mucus, he lost nearly 2 stone of his weight, and it is not surprising that he was miserable and depressed.

Treatment by vaccines was unsuccessful and he was transferred to Addington Park.

Case 2831, *Bomb. G.*—In February 1917, while the patient was in Salonica, he was taken ill with dysentery: that is 60 weeks ago, and he is still a carrier. He passed blood and mucus then and has done so ever since; as a rule, he has 1 formed motion every day, and 2 or 3 consisting of blood and mucus only. In November 1917 he was admitted to the 42nd General Hospital, Salonica, whence he was transferred to Imtarfa, where he was found to be a Shiga carrier, on Jan. 13, 1918. Since he was admitted to this hospital, on Mar. 28, 1918, his faeces have been examined 32 times and *B. dysenteriae* (Shiga) has been present on each occasion, usually constituting more than 50 per cent. of the colonies on the plate. He has been treated with a vaccine, but without benefit.

Case 2631, *Pte. Sh.*—This patient's last attack of dysentery commenced during May 1917, while he was in Egypt. He was admitted to the General Hospital at Cairo and subsequently to the General Hospital at Alexandria, from which he was sent to England, where he was admitted to the Hope Hospital, Manchester. From Manchester he was sent to the dysentery depot at Barton, and 1 week later he was sent to this hospital as a case of 'colitis'. Here Shiga's bacillus was found 25 times in 30 examinations. His stools contained blood and mucus, and, as he showed no signs of improvement after treatment with a vaccine, he was transferred to Addington Park War Hospital, 11 months after the beginning of his illness, still a carrier of dysentery bacilli. It is possible that his infection was of even longer duration, for he had suffered from recurrent diarrhoea in Egypt for a year before he went into hospital.

Case 2546, *Pte. Gr.*—This man has not returned to duty since he was admitted to hospital in India, with dysentery, 47 weeks ago, in March 1917. His illness really dates from October 1915, when he had his first attack of dysentery in the Gallipoli peninsula, and did not return to his regiment for 5 months. He

was sent home from Bombay in August 1917 and admitted to the Royal Victoria Hospital, Netley. From Netley he was sent to the depot at Barton, whence, after 2 negative examinations, he was sent here with the diagnosis of 'mucous colitis'. Gr. is a bricklayer by trade, and his normal weight is over 12 stone. When he came here he weighed 10 st. 4 lb. and was a neurotic invalid. Shiga's bacillus was found 5 times in 9 examinations of his stools, which always contained blood and mucus, and he was transferred to Addington Park as a chronic carrier.

Case 2912, *Cpl. P.*—In this case there is a history of dysentery which goes back for 10 years to 1908, when P. was first taken ill in Rawal Pindi. After he had passed through the acute stage of the attack he had frequent attacks of diarrhoea; his stools generally contained blood and mucus, and, because of this, he was discharged from the Army in 1910. After his discharge he went to Canada, where he was employed in some electric-lighting works at Medicine Hat, and, though he passed mucus occasionally, his health was fairly good. On the outbreak of war he re-enlisted and went to the Dardanelles, where the dysentery came on again, with the result that he was invalided to Malta in November 1915, and, later on, to England. In September 1916 he went to France, and in December he was admitted to hospital again, with dysentery, at Étaples. In August 1917 he returned to light duty, though he was passing mucus and sometimes blood as well, and in the beginning of March 1918 he was sent up the line. The dysentery then became very much worse, his bowels were moved 10 or a dozen times a day, and he passed a great deal of mucus and blood, in consequence of which he was sent to a stationary hospital, whence he was transferred here on April 26.

While he was in this hospital Shiga's bacillus was isolated 10 times in 22 examinations, after which he was transferred to Addington Park as a chronic carrier.

3. *Carriers of B. dysenteriae, Flexner.*

Infections by organisms of the Flexner group are not so frequently persistent as those of the Shiga type, but the actual number of persistent carriers of these two types which we have met with has been approximately equal because the majority of the convalescent patients came from the Western front, where dysentery is almost always due to Flexner infections.

It is, perhaps, best to make it clear at the outset that, in this report, we do not discriminate between the *B. dysenteriae* of Flexner and the *B. dysenteriae*, Y, of Hiss and Russell, but include both under the term 'Flexner's bacillus'. We have admitted to this group only those bacilli which conform to the following requirements: non-motile; non-liquefying; do not ferment lactose, saccharose, or dulcite; produce acid in mannite, glucose, and milk, the latter becoming alkaline in a few days; agglutinate with an immune serum to, at least, half the full titre. Forty-six of the strains isolated agglutinated to full titre, and 15 to half titre. About half the strains formed indol in peptone water.

Fuller particulars of those strains which were isolated from persistent carriers are given later in tabular form.

These persistent carriers were found in the course of the examination of 1,782 convalescents during the 12 months which ended May 1918. Sixty-one (3·43 per cent.) of these patients were carriers of dysentery bacilli of the Flexner type, and 13 of these were persistent carriers.

The convalescents who were examined during the 12 months in question had been taken ill, on an average, between five and six weeks before their admission to this hospital, and they were sent here with the following diagnosis:

Dysentery (including diarrhoea, colitis, and enteritis)	935
Diseases of the enteric group	294
P.U.O. and trench fever	456
Miscellaneous diseases	97
	1782

Organisms of the Flexner type were isolated from 52 of the 935 dysentery convalescents, i. e. 5·56 per cent., but only 9 carriers were found among the 847 patients who were recovering from other diseases, i. e. 1·06 per cent., and 6 of these 9 gave accounts of attacks of dysentery in the past.

The history of the dysentery carriers which we have seen in this hospital indicates a different geographical distribution of the Shiga and Flexner types. The proportion of Flexner carriers who had served in other countries than France was practically the same as that of all the 1,782 men examined, but nearly all the Shiga carriers had served in tropical or sub-tropical climates. The actual numbers are given in the following table. It appears that Flexner dysentery has a general distribution, but the Shiga type is rare on the Western front.

TABLE SHOWING NUMBERS OF MEN WHO HAD SERVED IN FRANCE AND IN OTHER COUNTRIES RESPECTIVELY.

All convalescents		
1331	had served in France only.	
451	„ „ other countries	= 25 per. cent.
1782		
Shiga carriers		
2	had served in France only.	
11	„ „ other countries	= 84 per cent.
13		
Flexner carriers		
45	had served in France only.	
16	„ „ other countries	= 26 per cent.
61		

Judging from our experience in this laboratory, dysentery bacilli are not excreted so constantly by Flexner carriers as they are by carriers of Shiga's bacillus. The 61 Flexner carriers were examined 1,803 times and the bacillus was found on 330

occasions, i.e. once in every 5·06 specimens. In the examination of the 13 Shiga carriers, 469 specimens were plated, and Shiga's bacillus was isolated 207 times, or once in every 2·26 specimens.

When a man is unfortunate enough to be a chronic carrier of Shiga's bacillus, he is generally too much of an invalid to do regular work of any kind; chronic infection with Flexner's bacillus, on the other hand, does not as a rule mean chronic dysentery, and the carrier may be quite fit for work though he will be prone to occasional attacks of diarrhoea when his resistance is reduced by exhaustion or unsuitable food.

Sometimes the initial attack is so slight that the patient does not know that he has ever had dysentery. The following is an example of a healthy, persistent carrier of Flexner's bacillus, who had had dysentery so slightly that the nature of his ailment was not recognized.

Case 2532, *Dvr. A.*—Still a carrier 18 months after onset.

This man was sent here convalescent from P. U. O., and, at the time of his admission, the excreta of all such patients were being examined with the object of determining if any large proportion of such cases was due to enteric group infections; so that it was only by chance that he was found to be a dysentery carrier. It was also a matter of chance that he was first examined while he was excreting dysentery bacilli and not during a barren intermission.

The patient had never, to his knowledge, suffered from dysentery; but, when he was questioned, he remembered that during the winter of 1916, while he was being treated for rheumatism in a hospital in France, he had a slight attack of diarrhoea and passed blood and slime, but he could not recollect that since then he had ever suffered from any looseness of the bowels. More than a year after this attack he was admitted to a hospital in France, on Dec. 15, 1917, with fever and pains in the back and limbs. On Jan. 29, 1918, he was sent here convalescent, with the diagnosis, as mentioned above, of 'P. U. O.'

B. dysenteriae, Flexner, was isolated from the second specimen of his faeces examined in this laboratory on Jan. 30, and, between that date and Mar. 29, it was found 31 times in 41 examinations, frequently constituting from 50 to 80 per cent. of all the colonies present on the plates. *E. histolytica* was never found.

This patient is a robust, ruddy-faced bricklayer of 21, who eats well and digests well, and is troubled by no such ailments as diarrhoea, constipation, or pains in the stomach; but, more than a year after his first and only attack of dysentery, an attack so slight that it was not recognized, he is still a carrier.

During the first 8 weeks he was in this hospital he excreted Flexner's bacilli in large numbers, then they suddenly disappeared and were not found again for a month, though 25 specimens of his faeces were examined during the interval; but at the end of the month, and just as he was about to be discharged, a single colony of Flexner's bacilli was found on the plate prepared from his faeces; the next day there were 2, and on the third day 60 per cent. of the colonies consisted of *B. dysenteriae*. He continued to pass dysentery bacilli for 5 days, and

then again there was an interval of a month, during which 14 negative samples were examined; at the end of this second intermission dysentery bacilli of the Flexner type appeared in his stools once more on June 3, 1918, more than 18 months after the slight attack of unrecognized dysentery which he had in the winter of 1916.

The statement is sometimes made that it is futile to examine faeculent stools for dysentery bacilli. This patient never passed blood or mucus while he was here; his case and many others which could be brought forward show that this statement is not correct.

This type of carrier is especially dangerous because, being in good health and capable of carrying on his ordinary vocation, he mixes in the life of his fellow men; he is the more dangerous because he passes dysentery bacilli occasionally and not regularly, which renders his detection a matter of great difficulty. There is no reason why the intervals of freedom, which in this patient lasted for 1 month, should not have lasted for 6 months or more, and yet, as in this case, the carrier may at other times excrete the infecting bacilli in vast numbers.

The following table shows the results of the examinations in this case, and the dates on which they were made. It can be seen how readily a carrier of this type may be overlooked, especially if only three or four specimens of the excreta are examined.

Table showing Results of Examinations of A.'s Faeces.

Jan. 30	0	March 1	+	April 1	0	April 27	0
31	+	4	+	2	0	29	+
		5	+	3	0	30	+
Feb. 2		6	+	4	0		
4	0	7	+	5	0	May 1	+
5	0	8	0	6	0	2	+
6	+	11	+	7	0	3	+
7	0	12	+	8	0	6	0
8	0	13	+	9	0	13	0
11	0	14	+	10	0	14	0
12	0	15	+	11	0	15	0
13	+	18	0	12	0	16	0
14	+	19	+	13	0	17	0
15	+	20	+	15	0	21	0
18	+	21	+	16	0	22	0
19	0	22	+	17	0	23	0
20	+	25	+	18.	0	24	0
21	0	26	+	19	0	27	0
22	+	27	+	20	0	28	0
25	+	28	+	22	0	30	0
26	0	29	+	23	0	31	0
27	+	30	0	24	0		
28	+			25	0	June 3	+
				26	0		

\+ = dysentery bacilli present.
0 = ,, ,, not found.

This intermittence is characteristic of Flexner carriers. As in the case of A. there are long intervals in which no dysentery organisms can be found in the faeces; but between the intermissions the patient excretes dysentery bacilli for a few days.

sometimes in large numbers. The two following are examples of persistent, healthy, intermittent carriers of this type:

Case 2115, *Pte. H.*—Still a carrier when transferred 5 months after onset.

This man's first and only attack of dysentery began suddenly in France, on Sept. 23, 1917, and lasted for 3 weeks.

When he was admitted here, on Nov. 8, as a 'walking case', he was a stone below his normal weight, but he soon regained what he had lost and added more to it. He had no diarrhoea while he was here, and, though 79 specimens of his excreta were examined, blood was never present, and on only 4 occasions was a little mucus found; yet he remained a carrier 5 months after the beginning of his illness.

As is shown in the following table, H. was an intermittent carrier; while he was here his faeces were examined, as far as practicable, every day for 4 months, and during that time there were 4 intermissions, during which no dysentery organisms were found in his stools. Between each intermission he would excrete Flexner's bacilli for two or three days and then stop suddenly. Three of the intermissions were of 3 weeks' duration, and one lasted for as long as a month.

TABLE SHOWING THE RESULTS OF EXAMINATIONS OF H.'S FAECES.

Nov. 9	+	Dec. 6	0	Jan. 4	0	Feb. 1	0
12	+	7	0	7	0	4	0
13	0	10	0	8	0	5	0
14	0	11	0	9	0	6	0
15	0	12	0	10	0	7	0
16	0	13	0	11	0	8	0
19	0	14	0	14	0	11	0
20	0	17	0	15	0	12	0
21	0	18	0	16	0	13	0
22	0	19	0	17	0	14	0
23	0	20	0	18	0	15	0
26	0	21	0	21	0	18	0
27	0	26	0	22	0	19	0
28	0	27	+	23	+	20	0
29	0	28	0	24	+	21	0
30	0	31	+	25	+	22	0
				28	0	25	0
Dec. 3	+	Jan. 1	0	29	0	26	+
4	+	2	+	30	0	27	+
5	+	3	0	31	0		

\+ = dysentery bacilli present.
0 = " " not found.

Case 2504, *L.-Cpl. L.*—Still a carrier when transferred 6 months after onset.

This man is another example of a chronic intermittent carrier. His attack of dysentery began on Dec. 8, 1917, and lasted for 3 weeks. *B. dysenteriae*, Flexner, was first isolated on Dec. 27. When he was admitted to this hospital, on Jan. 20, 1918, he looked strong and well, he had no abdominal pain, his stools were formed, and in 91 specimens examined here no mucus, pus, or blood were ever found.

Flexner's bacillus was isolated from only 8 of the 91 specimens examined in this laboratory (on Jan. 21, Feb. 15, Mar. 6 and 18,

Apr. 15, 16, and 25, and May 30). The longest intermission was 34 days, and during that period 18 specimens were examined with negative results. The last occasion on which *B. dysenteriae* was isolated was May 30, i. e. nearly 6 months after the beginning of his illness.

A table showing the results of the examinations made in this case is given below, and it demonstrates clearly that unless men who have suffered from bacillary dysentery are examined very frequently, and over long periods, carriers will escape detection.

What becomes of the bacilli during the intermissions is at present an open question. It may be that they are always present but are only discovered, by the methods at present employed, during a periodic increase in numbers; it may be that they lie hid in inaccessible parts of the intestinal system and appear in the faeces at intervals when they chance to escape; or it may be that Flexner's bacillus is not a fixed type in the intestine but may be derived, for instance, from a lactose-fermenting organism, and may emerge, on occasions only, as a typical dysentery bacillus.[1]

TABLE SHOWING THE RESULTS OF THE EXAMINATIONS OF L.'S FAECES.

Jan. 21	+	Feb. 25	0	March 28	0	April 24	0
23	0	26	0	29	0	25	0
24	0	27	0	30	0	26	0
25	0	28	0			29	0
28	0			April 1	0	30	0
29	0	March 1	0	2	0		
30	0	4	0	3	0	May 1	0
31	0	5	0	4	0	2	0
		6	+	5	0	3	0
Feb. 1	0	7	0	6	0	6	0
4	0	8	0	8	0	13	0
5	0	11	0	9	0	14	0
7	0	12	0	10	0	15	0
8	0	13	0	11	0	16	0
11	0	14	0	12	0	17	0
12	0	15	0	13	5	21	0
13	0	18	+	15	+	22	0
14	0	19	0	16	+	23	0
15	+	20	0	17	0	24	0
18	0	21	0	18	0	27	0
19	0	22	0	19	0	28	0
20	0	25	0	20	0	30	+
21	0	26	0	23	0	31	0
22	0	27	0				

\+ = dysentery bacilli present.
0 = „ „ not found.

Pathogenic protozoa have not been found more frequently in the excreta of carriers of dysentery bacilli than in the faeces of those who were not. In two of the persistent carriers there was a history of former findings of *E. histolytica* cysts at other hospitals. An account of these two is given in detail, although during their stay here they passed no *E. histolytica* cysts that we could detect.

[1] See also Douglas, Colebrook, and Morgan (1917): Medical Research Committee's Special Report Series, No. 6, p. 80.

It seems that when these men contracted bacillary dysentery, histolytica cysts, the vestiges of an old attack, were found in their stools and it was assumed that they were suffering from amoebic dysentery.

Case 2643, *L.-Cpl. Pr.*—Still a carrier 19 months after onset.

This man had his first attack of dysentery in December 1915, while he was in Egypt, but he appeared to have recovered from it, and in May 1916 he went to France, where he remained in good health until October, when he was taken ill suddenly, with vomiting, diarrhoea, and the passing of blood and slime. He was sent to England and admitted to Tootal Road Hospital, Manchester, where *E. histolytica* cysts are stated to have been found, and he was treated at the Hope Hospital with E.B.I.[1] and collosol argentum. In January 1918 he was transferred to the dysentery depot at Barton, whence he was sent here on February 20 suffering from chronic diarrhoea. In this hospital he was found to have 'ulceration of the rectum with commencing stricture' and appendicostomy was performed on February 25.

His faeces were examined 6 times without finding protozoa, but *B. dysenteriae*, Flexner, was isolated from the third specimen, and, between the date of his admission, on February 20, and May 14, it has been found in 39 out of 58 samples examined; on one occasion as many as 80 per cent. of the colonies on an Endo plate, spread with an emulsion of his faeces, consisted of Flexner bacilli.

It is possible, of course, that this patient's first attack, which occurred in Egypt during December 1915, was amoebic dysentery; but the second attack, in October 1916, was due to bacillary infection, for it began suddenly with vomiting and continued for months after all *Entamoebae* had disappeared from his stools. His faeces frequently contain blood and mucus, but though he is still a carrier, more than 18 months after his illness began, rest in hospital with careful dieting, and perhaps the daily washing of his intestine through the opening in his appendix, have brought about a great improvement in his general condition.[2]

Case 2750, *Pte. B.*—Still a carrier 10 months after onset.

This man, like the last, had been a carrier of *E. histolytica*, and, like him, he was a carrier of Flexner's bacillus.

He had suffered from dysentery in Johannesburg and on the West Coast of Africa some years before the War; but since then he had none until he was in France in July 1917, when he passed blood and mucus as he had done before, in Africa. He was sent home to England and admitted to East Leeds War Hospital, where *E. histolytica* cysts were found on August 20 and he was given a course of emetine bismuth iodide; 6 subsequent examinations of his stools proved negative and he was sent to the dysentery depot at Barton, where his stools were examined, again with negative results. He returned to France on Jan. 7, 1918, but from the time he left hospital he suffered from slight diarrhoea,

[1] E.B.I. = Emetine, bismuth, iodide.

[2] This patient was still a carrier of Flexner's bacillus in November 1918, more than two years after the beginning of his illness.

and he had not been in France a month before blood appeared in his stools again and he went to hospital once more.

He arrived here from France as a 'walking case' on March 15; 8 specimens of his faeces were examined but no cysts of *E. histolytica* were seen; *E. coli* was found on one occasion. *B. dysenteriae*, Flexner, was isolated from the eighth sample of his faeces, but was not found again until 3 weeks later, though 16 specimens were examined during the interval. In this case dysentery bacilli were present in small numbers and were isolated only 5 times in 32 examinations. The fifth occasion was on May 2, 1918, 10 months after the patient was first taken ill in France. He was then transferred from here to Addington Park as a chronic carrier. The patient was a burly man of 41, with ruddy cheeks (an appearance very different from that seen in a chronic carrier of Shiga's bacillus), but he was not really in good health, for blood and mucus were found in 7 of the 33 specimens examined, and it is interesting to note that from 4 of these 7 specimens dysentery bacilli were isolated.

TABLE SHOWING AGGLUTINATIONS, FERMENTATIONS, ETC., OF FLEXNER-TYPE ORGANISMS ISOLATED FROM PERSISTENT CARRIERS.

None of these strains fermented lactose, saccharose, or dulcite—none liquefied gelatine or was motile.

Name.	*Months since onset.*	*Glucose.*	*Maltose.*	*Mannite.*	*Dextrin.*	*Milk.*	*Indol.*	*Agglutination with C. 137.*	*Agglutination with C. 94.*	*Agglutination with own serum.*	*Agglutinin units, Oxford Flexner.*	*Agglutinin units, Oxford 'Y'.*
A.	16	A	AK^4	A	A^6	AK^4	$+^{14}$	1/3000	1/1000	1/80	6	0
B.	10	A	—	A	—	AK^6	—	1/1500	1/500	0	0	0
C.	?	A	AK^3	A	A	AK^5	$+^7$	1/6400	—	1/80	0	0
Co.	3	A	A	A	A	AK^6	$+^8$	1/1500	1/500	1/160	0	—
Fr.	8	A	—	A	—	AK^{10}	—	1/800	1/2000	1/40	6	—
H.	5	A	—	A	—	AK^7	—	1/2000	1/1000	1/320	10	0
K.	4	A	—	A	—	AK^5	$+^7$	1/3000	1/500	1/640	12	0
L.	5	A	AK^4	A	A^7	AK^5	$+^6$	1/12800	—	1/160	12	0
Lu.	6	A	—	A	—	AK^6	—	1/1500	1/2000	1/80	12	0
M.	3	A	A^7	A	A^5	AK^5	$+^{14}$	1/3000	1/1000	1/320	6	0
Pr.	18	A	—	A	—	AK^4	$+^{10}$	1/2000	1/2000	1/160	6	0
St.	3	A	A	A	A^3	AK^5	—	1/2000	1/5000	1/80	0	0
Sl.	3	A	A^4	A	A^5	AK^4	—	1/800	1/500	1/160	0	0

A = Acid. K = Alkaline. — = No change. + = Indol.

Numerals above letters indicate how many days after inoculation of medium the change took place.

Particulars of immune sera employed in diagnosis:

The 2 immune sera which were employed in carrying out the routine agglutinations of the strains isolated were C. 137 and C. 94 obtained from the Lister Institute of Preventive Medicine.

C. 137 had been prepared by employing 2 strains, 'Hiss & Russell, Y', and 'Ledingham, Y'.

The stated titre was 1/1500 for *B. dysenteriae*, Flexner, and the same for *B. dysenteriae*, Y.

Tested by the methods employed in this laboratory the titres of agglutination were as follows:

Strain Hiss & Russell, Y = 1/1500
„ Ledingham, Y = 1/3000
„ Flexner, Elstree = 1/800

C. 94 had been prepared at the Lister Institute with the strain 'Flexner, Elstree'.

The stated titre was 1/4000 for *B. dysenteriae*, Flexner.

Tested by the methods employed in this laboratory the titres of agglutination were as follows:

Strain Hiss & Russell, Y = 1/1000
„ Ledingham, Y = 1/500
„ Flexner, Elstree = 1/2000

We are indebted to the Director of the Lister Institute for kindly supplying us with cultures of 3 strains of dysentery bacilli used in these tests.

III. Group II. *Carriers of E. histolytica.*

When we began to make records of the histories of patients who were carriers, we did not take them down in much detail; but later on we extended our inquiries and we have collected fairly complete records of 122 carriers of *E. histolytica*.

We have divided them into 3 sub-groups:

(*a*) 55 who had only 1 attack of dysentery.

(*b*) 11 who had several isolated attacks of dysentery.

(*c*) 56 chronic cases.

Sub-group (*a*): 55 carriers of *E. histolytica* were admitted convalescent from a first attack of dysentery (in 17 instances the dysentery had been preceded by attacks of diarrhoea).

Only 2 of these men had been in tropical or sub-tropical regions; one had never been out of England; he was a corporal in the R.A.M.C. who had been on the staff of an ambulance train and had helped to move dysentery patients.

Sub-group (*b*): 11 carriers were admitted as convalescents after dysentery, whose records showed previous isolated attacks; 6 of them had been in tropical or sub-tropical countries. The following is an example of a case in this group:

Case 2085, *Cpl. H., aged* 23; *admitted Oct.* 31, 1917, *as convalescent from dysentery.*—He has never been in the East. His first attack of dysentery came on in France, November 1916. He was in hospital for 2 months there, but did not come to England. He had no further attack until August 1917, when he was passing

blood and mucus. Bacteriological tests in France were negative. At this hospital the cysts of *E. histolytica* were found in his faeces, Nov. 1, 1917, and he was transferred to Addington Park. Nov. 15, 1917.

Sub-group (*c*): 56 carriers were chronic cases; using the term chronic, as defined in the introduction to this paper, to mean a man who, for a period of more than 1 year, has suffered from repeated attacks of dysentery, linked up by less acute diarrhoea and the occasional passage of blood and mucus.

Only 25 per cent. of the 1,782 convalescents examined had ever been in any other country but England and France; in contrast with this, 48, or 82 per cent., of these 56 chronic cases had, at one time or other, served in tropical or sub-tropical regions.

Sixteen of the chronic cases had suffered from dysentery before the beginning of the War, and never had been free from it since the first attack. Eight of these 16 contracted the disease in India. 3 in China, 2 in Australia, and 3 in other countries. The 2 following are examples of these long-standing, chronic cases: such men manage to keep fairly well while they can diet themselves and lead quiet lives, but their health soon breaks down under adverse conditions.

Case 2660, *Pte. R., aged* 30*; admitted Mar.* 5, 1918, *as convalescent from amoebic dysentery.*—He first had dysentery in 1912, when in China. For 3 years after that he had dysentery on and off. When he went to the Dardanelles in 1915 he got so bad with it that he was obliged to go sick. He was treated in the field. From Gallipoli he went to Salonica, 1915, and to Serbia. He continued to suffer from dysentery, and when he went into hospital for malaria at Salonica he was treated for dysentery as well. He was sent on to Malta, and had emetine injections, September 1916. Thence he was sent to England, where he was in hospital at the 4th Southern General, Plymouth; he was discharged from hospital, November 1916. He rejoined his regiment. While on leave, May 1917, he went sick with an attack of malaria to the 4th London General. There he was treated for dysentery with cachets that made him sick. He left hospital Aug. 10, 1917, went back to his regiment, and was drafted out to France 14 days later. He suffered with diarrhoea and blood in his stools on and off the whole time he was in France, until at last he went sick, Jan. 28, 1918. '*E. histolytica* vegetative' was found in his faeces in France, and he was given 2 courses of E.B.I. powders at the 52nd Stationary Hospital. He was then sent to England. At this hospital he was found still to be passing the cysts of *E. histolytica*, Mar. 11, 1918, and he was transferred to Addington Park, Mar. 20, 1918.

Case 2522, *Bdr. C., aged* 31*; admitted Jan.* 22, 1918, *as convalescent from dysentery.*—When in Hong-kong, 1913, he was in hospital 2 or 3 times with diarrhoea; he passed blood and mucus. He went to France in August 1915, and in October had an attack of dysentery. He was invalided to the Royal Victoria Hospital, Boscombe. He went back to his depot in February 1916. He went to the Isle of Wight, and in May 1916 he had an attack of

dysentery for which he was invalided to Parkhurst Hospital. He returned to duty at Gosport, June 1916. But he still had diarrhoea, and in September he was sent to Cosham Hospital. He returned to duty in October, and went to Salisbury. He was drafted to France in January 1917. He had had diarrhoea all the time he was at Salisbury, and he was put into hospital 2 days after landing in France, and kept there until March. Then he was sent home to Alfred Street Hospital, Manchester. He went back to his depot, May 17, 1917. On July 29 he was sent to the Isolation Hospital, Southampton, and he was transferred from there to Netley in September 1917. He was sent to Barton-on-Sea in October. Thence to Mont Dore Hospital, Bournemouth, where he had a course of E.B.I. pills for 12 days, Nov. 3, 1917. He was returned to Barton, and had there a 20 days' course of E.B.I. pills, Dec. 24, 1917. He was transferred from Barton to this hospital, and was found to be still passing the cysts of *E. histolytica*, Jan. 30, 1918. He was transferred to Addington Park, Feb. 18, 1918.

Of the chronic cases with shorter histories, 2 had been taken ill in 1914 (1 in Australia and 1 in West Africa); but no fewer than 23 dated the onset of dysentery from 1915. Eighteen of these 23 had contracted the disease in the Dardanelles, 3 in Egypt, 1 in Mesopotamia, and 1 in France. The 3 patients whose histories follow are given as examples of cases that contracted the disease in the Dardanelles:

Case 2720, *L.-Cpl. V., aged* 26*; admitted Mar.* 14, 1918, *as convalescent from dysentery.*—He first had dysentery at Gallipoli, October 1915. He was invalided to Malta, and thence to Fulford Road Hospital, York, December 1915. He was there for a month, then went on leave. On returning to his depot he was sent to convalescence at Shoreham-on-Sea. There another attack of dysentery came on and he was sent to Hove Hospital. He went back to his depot, but all the time he remained in England he suffered from diarrhoea. He went out to France in July 1916. He had an attack of dysentery in February 1917, and was invalided home to Queen Mary's Military Hospital, Whalley, where he stayed 5 weeks. He was then transferred to Tootal Road Hospital, Manchester. He went to Barton-on-Sea in May 1917, and was sent out to France again in July. The dysentery came on again very badly, and he went sick 3 days after landing. He was sent to the 1st Southern General Hospital, Birmingham, where he was given 12 days' E.B.I. He went on to Barton in October 1917, and was drafted to France for the third time, Jan. 17, 1918. Three days after landing in France he once more went sick with dysentery; he was passing blood and mucus and was 'very bad'. He says he has never been free of the trouble since he first had dysentery in Gallipoli, 1915. The tests at this hospital showed the presence of *E. histolytica* cysts in his faeces. He was transferred to Addington Park, Mar. 25, 1918.

Case 2703, *Pte. W., aged* 34*; admitted Mar.* 11, 1918, *as convalescent from amoebic dysentery.*—He had dysentery first at Gallipoli, December 1915. He was invalided to Egypt, and was in Giza Hospital, near Cairo, January 1916, for three weeks.

Thence to Abbassiah (?) and the Embarkation Rest Camp, Gabbarra, Alexandria. From there he was sent to a convalescent Rest Camp near Alexandria, March 1916, and then, still having dysentery, he was sent to the General Hospital, Alexandria, where he had two 'positive' examinations. He left that hospital on Mar. 24, 1916, and went to France, landing there on Apr. 1, 1916. He suffered from dysentery, with blood and mucus, at Calais; and when he went up the line he got so bad that he was sent down to be recategorized at Advance Base, Calais. He was declared unfit, and sent to England pending discharge, Jan. 17, 1917. In England he was examined at Southport and there recategorized A 3, and he went on to Bath, where he was marked A 1. He was reporting sick continually with weak bladder and dysentery; however, he went out to France again on Jan. 2, 1918, and after eleven days in trenches was obliged to go sick once more on Jan. 20, 1918. *E. histolytica* was found in his faeces in France, Feb. 27, 1918, and he was given 5 days' emetine pills and injections; the treatment had to be stopped, as he vomited so much. The cysts of *E. histolytica* were found in his stools at this hospital, Mar. 14, 1918; he was given a course of E.B.I. pills and transferred to Addington Park (Mar. 30, 1918). He says he has never been free of dysentery since 1915, and has lost two stone in weight.

Case 1792, *Pte. B., aged 22; admitted Sept.* 9, 1918, *as convalescent from dysentery.*—He first had dysentery in Gallipoli, and was sent from there to Malta, September 1915. Thence to England, where he was in hospital at Sheffield and Doncaster. At Doncaster his illness was diagnosed as Shiga dysentery. He went out to France. In October 1916 he was again invalided with dysentery (Shiga). He was sent to England, and in hospital at Mont Dore and Barton he was diagnosed amoebic dysentery, and given injections of emetine. He went out to France again, and had a third attack, Aug. 8, 1917, with which he was once more invalided to England. Two tests in France were negative, July 27, 1917, and Aug. 24, 1917. In this hospital the cysts of *E. histolytica* were found in his faeces, and he was given a course of E.B.I. capsules. This failed to clear him, and he was transferred to Addington Park, Oct. 8, 1917.

IV. Group III. '*Negative*' *Cases.*

As a control to the histories of the bacillary and the amoebic carriers we recorded the histories of 42 convalescents in whose excreta we found no bacillary or protozoal cause of disease, and, to our surprise, 40 per cent. of them gave a history of chronic dysentery.

For convenience we have classified these patients in three sub-groups, as we did when considering the amoebic carriers:

(*a*) 21 who had only one attack of dysentery (in 13 instances this had been preceded by diarrhoea).

(*b*) 4 who had several isolated attacks.

(*c*) 17 chronic cases.

The first two sub-groups are not of special importance to our present thesis. Sub-group (*c*) consisted of 17 chronic cases. Eight of these men, all of whom had been in tropical or sub-tropical countries, were first taken ill in 1915, and in four of them *E. histolytica* had been found during the course of their illness, though the examinations made while they were here proved negative. Four men dated their dysentery from 1916 and 5 from 1917.

Five had served in France only; 4 had been in Gallipoli; 4 in Africa; and 4 in Salonica, Mesopotamia, India, and South America respectively.

In 11 of these 17 chronic cases no cause for their dysentery had been found, so far as their records showed, throughout the course of their illness, and the following are examples of such:

Case 2607, *Gnr. Sm., aged* 38; *admitted Feb.* 17, 1917, *as convalescent from dysentery.*—He had dysentery in Gallipoli, 1915, and was invalided to Malta, where he was given emetine injections. In February 1916 he went to Mile End Military Hospital, London, and then to Woolwich Hospital, where he remained until August 1916. He went back to his depot, and to France in January 1917. Dysentery continued all the time he was in hospital, and it began again in June 1917 in France. He reported sick with it two or three times, but received treatment with pills in the field, and returned to duty. Things got gradually worse, until at last he reported sick on Jan. 14, 1918, passing blood and mucus, and was sent to hospital. Two tests in France were negative (Jan. 28, 1918, and Feb. 1, 1918), and the serum reaction was negative (Feb. 2, 1918). The tests at this hospital were negative. He was transferred to the dysentery depôt at Barton on Mar. 26, 1918.

Case 2632, *Pte. H., aged* 41; *admitted Feb.* 22, 1918, *with mucous colitis.*—He first had dysentery at Salonica in August 1916. He was at the Fifth Canadian Hospital, Salonica, for 6 weeks, and then for 5 weeks at Malta. Thence he was sent to Steppinghill Military Hospital, Stockport, in December 1916. He went to Addington Park in the end of December, and remained there 5 months; he had 1 course of E.B.I. pills. Thence he went to Barton-on-Sea for 3 weeks, and then on leave. Then he was sent to a training camp at Withernsea, Yorkshire, and there he had 3 weeks' treatment for dysentery at St. John's V.A.D. Hospital. He went out to France on Sept. 23, 1917. In France the dysentery began again at once, and he was sent to a segregation camp for 3 tests. From there he went to the Stationary Hospital at Étaples for 10 weeks. He was sent to England after that, and was at Addington Park for a month, February 1918, and thence was sent to Barton-on-Sea, where he remained a week. His tests at Barton were negative, and he was transferred to Southampton for 'blood-stained mucous colitis'. He says he has had dysentery all the time since the attack in 1916, and has never felt fit since. The tests at this hospital were negative, and he went on furlough Mar. 28, 1918.

Case 2695, *Pte. Gr., aged* 19; *admitted Mar.* 10, 1918, *as convalescent from dysentery.*—He landed in Mesopotamia in February 1916, and had dysentery there in July 1916. He did not go sick for a month, but things grew intolerable, and he was obliged at

last to give in. He was passing blood and mucus. He had two courses of emetine injections, and was invalided to Cumballa Hospital, Bombay. From there he went to the General Hospital, Alexandria, at the end of August 1916. He remained there until October, and then was sent to England, where he was in the Klyne House Hospital, Manchester, for about 6 weeks. He went to Barton-on-Sea, and from there (Jan. 26, 1917) on sick leave. He rejoined his battalion on Feb. 5, 1917, and while still in England suffered from slight diarrhoea in April and August. He was drafted to France, Oct. 19, 1917, and there he was quite fit until about Jan. 22, 1918, when the dysentery began again. He hung on until Feb. 3, 1918, when he was obliged to go sick. A bacteriological test in France was negative (Feb. 17, 1918); the serum reaction (Feb. 17, 1918) gave 9 units Flexner. The tests at this hospital were negative, and he was cleared to Barton-on-Sea (Mar. 26, 1918).

In 6 of the 17 chronic cases *E. histolytica* had been found previously, during the patients' illness, before they came to this hospital, and they had been treated with emetine or with the double iodide of emetine and bismuth; the following are examples of such cases:

Case 2536, *Pte. D., aged 24; admitted Aug.* 13, 1917, *and Jan.* 29, 1918, *as convalescent from amoebic dysentery.*—He had been to the River Plate on the Allan Line boats before the War, but never had any dysentery there. Dysentery, with blood and mucus, began in France, Dec. 29, 1916. He was invalided to Mill Lane Hospital, Manchester, Jan. 17, 1917, and to Croydon Feb. 10, 1917. He was transferred from there to Barton-on-Sea, which he left in May. He went out to France again, and dysentery began July 8, 1917, with blood and mucus. The cysts of *E. histolytica* were found in his faeces, and he was given E.B.I. from Aug. 8, 1917, to Aug. 13, 1917, when he was sent to the University War Hospital, Southampton. After 7 negative examinations here he was sent (Aug. 28, 1917) to Barton. He had 10 days' leave, September 1917, and then was for 7 weeks at his depot in Aberdeen. He went out to France, Dec. 4, 1917, went up the line, and reported sick with dysentery Dec. 16, 1917. It was the same sort of attack as before, and came on gradually. He was ill 3 days before going sick. He was invalided to England, to the University War Hospital, Southampton. The examinations here were negative. He was cleared and sent to Barton-on-Sea, Feb. 26, 1918.

Case 2634, *Pte. P., aged 32; admitted Feb.* 26, 1918, *with diarrhoea following dysentery.*—His first attack of dysentery came on in France gradually for 3 weeks during January 1917. He went sick at last, Feb. 8, 1917, and was sent to England, to Belmont Road Military Hospital, Liverpool, on Mar. 12, 1917. He was transferred from there to the Tropical School Hospital as a carrier, April 1917. He was in the Tropical School Hospital for 5½ months, and was given E.B.I. pills and emetine injections, but remained positive all the time. He was sent to Southport Convalescent Home in September 1917. He returned to Belmont Road Hospital, Liverpool, in October, and was found to be still positive. He remained at that hospital till Feb. 1, 1918, when

he was transferred to Barton-on-Sea; and from Barton he was transferred to Southampton with diarrhoea following dysentery. He says he has had diarrhoea alternating with constipation now for more than a year, and passes blood and slime occasionally. He has never been in the East. Five bacteriological and 12 protozoological examinations were made at this hospital, but, except for the presence of *Lamblia* cysts, they were negative. He went on furlough Mar. 28, 1918.

While we have taken a great deal of pains to examine our cases thoroughly (each case had at least 6 examinations for protozoa), we do not pretend that a number of carriers may not have escaped our net. Had time and hospital accommodation permitted of our examining these 'negative' men still further, we should almost certainly have lit on the causal organism in a small percentage of them.

On the other hand, it seems probable that in some cases the intestine has been so seriously damaged that the patient is still liable to dysentery after the original cause of it has disappeared.

It is important, also, to bear in mind that the symptoms of chronic dysentery are not always due to bacillary or protozoal infection. The following case is a good example of this:

Case 2914, *Gnr. B., aged* 37.—Dysentery began in 1915 while he was on the Suez Canal, and for about 4 weeks he was passing blood and mucus. A few months later he went to France, and while there he suffered from frequent attacks of diarrhoea, and occasionally passed blood.

Towards the end of 1916 he was wounded by shrapnel and was sent to England, where he remained until 1918. All the time he was in England he was troubled with occasional attacks of diarrhoea, and frequently passed blood and mucus.

At the beginning of 1918 he was sent to France again, but the dysentery became so severe that he was admitted to hospital and shortly afterwards transferred to England with the diagnosis 'amoebic dysentery (carrier)'.

He was admitted to this hospital on Apr. 28, 1918. Sixteen negative bacteriological examinations were made, and Miss Margaret Jepps searched 18 specimens of his faeces without finding *E. histolytica*. His stools frequently contained blood and pus, but he improved, and he was sent to the dysentery depot at Barton on May 25. About a fortnight later he was sent back, because he was passing blood and mucus again. His excreta were repeatedly examined for dysentery bacilli and for protozoa, but still the results were negative. At length an examination of his rectum was made, and he was found to be suffering from carcinoma.

V. Summary and Conclusions.

(1) During the 12 months ending May 31, 1918, 935 dysentery convalescents and 847 patients who were convalescent from other diseases, such as enteric and trench fever, were examined in this laboratory.

(2) Of 229 dysentery convalescents whose histories were taken—
112 were convalescent from a first attack of dysentery.
29 had had 2 or 3 isolated attacks.
88 were 'chronic' cases.

(3) 61 were carriers of *B. dysenteriae*, Flexner.
13 were carriers of *B. dysenteriae*, Shiga.
122 were carriers of *E. histolytica* (9 of these were also bacillary carriers).
42 were 'negative'.

(4) The majority of the long-standing cases had been, at one time or other, in the tropics or the near East.

Of the 112 cases convalescent from a first attack of dysentery, only 11 (= 9·8 per cent.) had been in tropical or sub-tropical regions.

Of the 29 cases with several isolated attacks in the past, 14 (= 48·3 per cent.) had been in tropical or sub-tropical regions.

Of the 88 chronic cases, 74 (= 84·1 per cent.) had been in tropical or sub-tropical regions.

(5) Most of the 88 chronic cases had suffered from recurrent attacks of dysentery over long periods.

4	had had	dysentery	at intervals since	1904
1	,,	,,	,,	1905
2	,,	,,	,,	1906
2	,,	,,	,,	1909
1	,,	,,	,,	1911
2	,,	,,	,,	1912
5	,,	,,	,,	1913
4	,,	,,	,,	1914
37	,,	,,	,,	1915
18	,,	,,	,,	1916
12	,,	,,	,,	1917
88				

(6) In these long-established cases relapses are frequent, and we are convinced, from consideration of these patients' histories, that, in the Army, dysentery is a serious cause of inefficiency.

The hopelessness of sending these men back to active service in the field is, we think, not sufficiently recognized. Their continual relapses and returns must involve a great deal of labour and expense, and must tend to clog the military hospitals unnecessarily.

The hardships to the men themselves are often needlessly severe.

The repeated relapses, under service conditions, tend to reduce a man to chronic invalidism who might, in easier circumstances, be able to avoid the frequent acute return of the trouble.

(7) In the group of 935 dysentery convalescents, 71 or 6·95 per cent. were found to be carriers of dysentery bacilli; 26 or 2·78 per cent. were persistent carriers.

Fifty-eight were Flexner carriers (5·56 per cent.) and 13 were Shiga carriers (1·39 per cent.).

(8) In the group of 847 non-dysentery convalescents there were 9 carriers of dysentery bacilli (1·06 per cent.), and 6 of these gave a history of dysentery. These 9 were all Flexner carriers.

(9) The 13 Shiga carriers were all persistent carriers.

(10) Thirteen out of 61 Flexner carriers were persistent carriers.

(11) All the Shiga carriers suffered from chronic dysentery and mental depression, and were unfit for work.

(12) With two exceptions the carriers of Flexner's bacillus were in fair health and fit for work, under favourable conditions.

(13) Twenty-five per cent. of all the patients examined had served in other countries besides France; but all the Shiga carriers except 2 had been in tropical or sub-tropical countries.

(14) The Flexner carriers came from France and from other theatres of war in approximately equal proportions.

(15) The infecting organism is more constantly present in the faeces of Shiga carriers than in carriers of *B. dysenteriae*, Flexner.

Sixty-one Flexner carriers were examined 1,803 times, and the bacillus was found on 330 occasions, i.e. once in every 5·06 specimens.

Thirteen Shiga carriers were examined 469 times, and Shiga's bacillus was isolated 207 times, or once in every 2·26 specimens.[1]

(16) One of the chief characters of persistent infections with Flexner's bacillus is intermission. The organisms are found in the stools for 1 or 2 days in succession, and then there is frequently an intermission of 4 or 5 weeks, during which all the examinations are negative; but at the end of that time the bacilli appear again. This renders the detection of a Flexner carrier a matter of difficulty, and makes it almost impossible to say when a patient has ceased to be a carrier.

(17) Men who have been carriers of Shiga's bacillus for more than 3 months are not likely to be of further use as soldiers; when an attempt is made to employ them as such they generally break down in a short time. It is better for the Army and for themselves that they should be discharged and placed under the supervision of the Civil Health Authority.

(18) Men who are still carriers of Flexner's bacillus more than 3 months after the commencement of an attack of dysentery should be employed in England for a period of 6 months. Their Commanding Officer should be notified that they should not be employed in handling food. At the end of 6 months they should be sent to hospital for 2 weeks, where their stools should be examined at least 6 times. (Professor Glynn has recommended (Medical Research Committee, Special Report Series, No. 7, p. 104) that all 'cured' dysenterics should be sent to the Command Depot, where two tests of the faeces should be made at intervals of about a month.)

(19) Dysentery patients who are not found to be carriers, if they have records of several attacks of dysentery extending over a period as long as 2 years (more especially where the acute attacks have been linked up by diarrhoea), should either be discharged from the Army, when their dysentery has subsided, or should be placed in a lower category in the Army.

(20) The examination of dysentery convalescents should be carried out in laboratories attached to the hospitals where the

[1] See also Rajchman and Western: Medical Research Committee's Special Report Series, No. 5, pp. 63, 73.

patients are treated; not only because dysentery bacilli are quickly overgrown, where there is delay in the examination of the specimens, but more especially because it is of the greatest assistance to the laboratory worker to be able to deal directly with the patient.

(21) The Medical Officer in clinical charge of the patients should work under the direction of the officer in charge of the laboratory. The latter will then be kept informed of the condition of the men, and the former, by seeing what is being done in the laboratory, will be able to obtain an insight into the carrier problem, and will be led to take a keener interest in what is, to him, the very dull task of looking after convalescent patients.

We wish to record our great indebtedness to Lieut.-Col. Lauder, R.A.M.C., the officer in charge of this hospital, without whose tact and assistance it would have been impossible to carry out these investigations.

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INTRODUCTION

THE following Report upon the Flexner-Y group of dysentery bacilli gives the results of long and patient work by the late Dr. H. S. Gettings so far as it has been found possible to retrieve them from his laboratory note-books and other papers as these were found after his sudden and untimely death, on June 15, 1918. The work of arranging them for the press has been kindly undertaken for the Committee by Captain S. R. Douglas.

The circumstances in which these investigations were begun and continued are mentioned by Captain Douglas in his introduction to the report. In spite of an inherited physical infirmity, Dr. Gettings gave to his work a prolonged patience and skill that won the respect of all who knew him. The lines of inquiry he followed were leading to many points of scientific interest and they gave promise of practical gains in the improved control of disease. It is part of the tragedy of his untimely death last June that he should thus have failed to reap the harvest of these preliminary studies himself and to bring his results into application to the object he had kept so long in view—the prevention and control of dysentery in asylums and other communities. It is further to be deplored that it did not fall to him even to present his own account of the work he had completed at the time of the accident which led to his death. In great part his notes were in such order that his findings could be given with confidence by one who, like Captain Douglas, had worked side by side with him and knew the details of his methods; but we have lost much, no doubt, that Dr. Gettings had in mind at the time for publication.

The material he left shows clearly, however, that after trial and rejection of cultural and of ordinary agglutination methods for distinguishing clearly between different sub-groups of Flexner dysentery bacilli, he had by means of tests based on the absorption of agglutinins obtained sharp discrimination between four sub-groups, of which one appeared to be identical with the so-called Y group previously described. Dr. Gettings's clear recognition of these four sub-groups, which he had discussed freely with other

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workers, has already given aid to the recognition of organisms of the Flexner group whose characters had been found elsewhere to be 'aberrant' or which had missed detection. Further work by others is already being applied to bringing knowledge of these sub-groups into use for diagnostic purposes and for preventive work.

The Committee are greatly indebted to Captain Douglas for the pains he has given to the preparation of Dr. Gettings's notes for this report. All who know the relation of laboratory records to a finished paper will appreciate at once both what we may have lost in losing Dr. Gettings's own presentation of his results, and what is owed to Captain Douglas for his care in doing this office for his fellow worker.

MEDICAL RESEARCH COMMITTEE,
15 Buckingham Street,
Strand, W.C. 2.

January 30, 1919.

AN INVESTIGATION OF THE FLEXNER-Y GROUP OF DYSENTERY BACILLI

ISOLATED FROM CASES OF ASYLUM DYSENTERY OCCURRING AT WAKEFIELD ASYLUM, WITH SPECIAL REFERENCE TO THE POSSIBILITY OF SUB-DIVIDING THIS GROUP OF BACILLI.

By the late H. S. Gettings, L.R.C.P., L.R.C.S. Edin., D.P.H.

Arranged for the press by S. R. Douglas, M.R.C.S., L.R.C.P. (Capt. I.M.S., retd.)

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I. Introduction.

During the period (1912–16) in which he was Pathologist at the Wakefield Asylum Dr. H. S. Gettings made an extended study of asylum dysentery. Some of the results were embodied in the following papers:

(1) Dysentery. Past and Present. *Journal of Mental Science*, 1913, October.

(2) The Detection of a Dysentery 'Carrier'. *Journal of Mental Science*, 1914, October.

(3) Bacillary Dysentery. *Trans. Soc. of Tropical Med. and Hyg.*, 1915, Vol. VIII, No. 4.

In the first paper, which is one of great interest, he was able to show from an examination of the historical records of the Wakefield Asylum that dysentery had never been absent from that institution for any long period since its foundation. Reasoning from these and other facts found in the records, he came to the conclusion that the disease was probably kept 'alive' by the agency of 'carriers'.

In the second paper, which was published a year later, he was able to confirm this opinion from the study of a small outbreak of dysentery which was traced to a 'carrier'. This 'carrier' had most probably been the cause of other small outbreaks.

During the time he was occupied in investigating the cases of dysentery he collected a large number of strains of the Flexner-Y group of dysentery bacilli. While still acting as Pathologist of the Asylum he began to examine the various strains of this group of bacilli, his object being to ascertain whether they all fell into a single group or could be divided into a number of sub-groups.

In view of the importance of this work, in relation not only to the problems of asylum dysentery but also to the study of dysentery among our Forces overseas, the Medical Research Committee in 1915 invited Dr. Gettings to give his whole time, on their behalf, to the continuation of his inquiries. Early in 1916 they were able to obtain laboratory accommodation for him by the courtesy of the Inoculation Department, St. Mary's Hospital, and here his work progressed so well that, in spite of interruptions due to some other inquiries of more urgent importance which he undertook and completed,[1] it had reached its final stage at the beginning of 1918.

From February of this year, in consequence of an injury received in a railway accident, Dr. Gettings was laid up for some months. By June he had, however, seemingly almost completely recovered when he suddenly became seriously ill, and greatly to the regret of all his associates, this illness proved fatal on June 15, 1918.

In order that the record of this work—the result of many years careful and accurate experimentation—should not be lost, the Medical Research Committee, with the consent of his relatives, requested me to examine Dr. Gettings's papers and, if possible, to write a report on the work so far as it was completed. It was with considerable trepidation that I consented to attempt this task, knowing the difficulty of following the notes of another worker. However, on examination, Dr. Gettings's records were found to be so fully and clearly stated that I have been able to follow the details of the various experiments. In addition I had the further advantage of having, in the past, often discussed the work with him. I hope that the following report may give his more important results. If this aim is attained I shall be content, as it will indicate that many difficulties, at first seemingly unsurpassable, have been overcome. It is, however, quite impossible to hope that all the points will be given, or that this report will compare in value with that which Dr. Gettings would himself have compiled, as probably

[1] The result of this work appeared in No. 15, Special Report Series of the Medical Research Committee, 1918.

many of his ideas and facts were never placed on record in his note-books.

II. Object of the Inquiry.

The object of the work was to ascertain if the Flexner-Y group of dysentery bacilli could be divided into a number of sub-groups, and Dr. Gettings evidently asked himself the following questions:

I. Is it feasible to do this by the study of the biochemical reactions of the bacilli?

II. Is it feasible to do this by the study of either of the following reactions of immune sera?

(*a*) The agglutination of emulsions of the bacilli by a serum made by inoculating animals with a vaccine prepared from a single strain.

(*b*) The absorption by the various bacilli of the specific agglutinins from a serum prepared by means of a single strain of the bacilli.

III. Biochemical Reactions.

Is it possible to divide the members of the Flexner-Y group of bacilli into a number of sub-groups by the study of their biochemical reactions?

Technique, &c.

Plates were made from the emulsified faeces on MacConkey's bile salt lactose neutral red agar, and after incubation a number of the white colonies were picked off and pure cultures made. These were then planted in lactose broth, litmus being used as the indicator, and the broth being made with the meat extract and peptone.

If the bacillus was found not to ferment lactose after incubation for at least seven days, the following tests were made.

The bacillus was planted in broths containing (i) glucose, (ii) mannite, (iii) dulcite, (iv) saccharose, (v) salicin. These were incubated for at least seven days and examined daily for any fermentation reactions. Cultures were also made into litmus milk and into peptone water; the milk culture was incubated for fourteen days and examined at intervals for the presence of acidity or any other change of reaction and also for clotting; the peptone water culture was incubated for seven days and then tested for the presence of indol.[1]

It will be seen that the scheme of these tests is that recommended by C. J. Lewis, *L. G. B. Report*, 1910–11. These tests having been completed, any strains that produced acid in glucose and mannite

[1] The exact method used in this test I have been unable to ascertain. S. R. D.

broths but failed to ferment dulcite, saccharose, and salicin were provisionally classed as members of the Flexner-Y group. The results of the other two tests, as will be shown later, were not quite constant, but usually indol was present in the peptone water culture and the milk culture remained alkaline. The provisional diagnosis was confirmed by finding that emulsions, made usually from young agar cultures, were agglutinated by a polyvalent agglutinating serum for the Flexner-Y group.

In attempting to split the various strains, which had been collected, into sub-groups by means of biochemical reactions Lewis's 'secondary series' of sugars were employed. These consist of (i) sorbite, (ii) rhamnose, (iii) maltose, (iv) levulose, (v) galactose, (vi) mannose, (vii) raffinose, (viii) dextrin, (ix) inulin, (x) adonite, (xi) glycerin.

Using these tests, the results obtained by investigating 285 strains of the Flexner group isolated from cases were recorded.

On examining these results it is at once obvious that it is quite impossible to divide this group of bacilli into sub-groups by such reactions, and in the following five tables sufficient results are given to show the uselessness of this method.

In Table I, the results are given of the fermentation reactions, &c., of thirty-six strains each isolated from a single case; those strains being selected which were afterwards used in the second portion of this research in carrying out agglutination and absorption tests.

The following signs and abbreviations are used in these tables:

A indicates that the carbohydrate in question, or milk culture, was fermented, acid being formed.

— indicates that the carbohydrate was unaffected or that the indol test was negative.

+ indicates that the indol test was positive.

Alk indicates that the milk culture remained alkaline, the alkalinity being increased if any change occurred.

A & C indicates that acid and clot were produced in the milk culture.

Dcl indicates that there was decolorization of the litmus used as an indicator.

s following A indicates slight production of acid.

TABLE I

		Primary Series							Secondary Series											
No. of Case	No. of Strain	Glucose	Mannite	Dulcite	Saccharose	Salicin	Indol	Milk—14 days	Sorbite	Rhamnose	Maltose	Levulose	Galactose	Mannose	Raffinose	Dextrin	Inulin	Adonite	Glycerin
1	5	A	A	—	—	—	—	A	—	—	—	A	A	A	A.s	—	A.s	—	—
6	1	A	A	—	—	—	—	A	—	—	A.s	A	A	A	A	A.s	—	—	—
7	1	A	A	—	—	—	—	A	—	—	A	A	A	A	A	—	—	—	—
8	1	A	A	—	—	—	—	A	—	—	A	A	A	A	A	A	—	—	—
9	1	A	A	—	—	—	+	Alk	—	—	A	A	A	A	A	A	—	—	—
10	1	A	A	—	—	—	—	Alk	—	—	—	A	A	—	A	—	—	A	—
11	1	A	A	—	—	—	+	Alk	—	—	—	A	A	—	A	—	—	A	—
17	1	A	A	—	—	—	—	Alk	—	—	—	A	A	A	A	—	—	—	—
19	1	A	A	—	—	—	—	Alk	—	—	A	A	A	A	A	—	—	—	—
22	1	A	A	—	—	—	—	Alk	—	—	A	A	A	A	—	—	—	—	—
23	1	A	A	—	—	A	—	A & C	—	—	—	A	A	A	A	—	—	—	—
24	1	A	A	—	—	—	+	Alk	—	—	A	A	A	A	A	Del	—	—	—
26	1	A	A	—	—	—	+	Alk	—	—	A	A	A	A	—	—	—	—	—
28	1	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
38	1	A	A	—	—	—	+	A	—	—	—	A	A	A	—	—	—	A	—
39	1	A	A	—	—	—	+	A	—	—	A	A	A	—	—	—	—	A	—
40	1	A	A	—	—	—	+	A	A	—	A	A	A	—	—	—	—	A	—
47	1	A	A	—	—	—	—	Alk	—	—	—	A	A	A	A	—	—	—	—
48	1	A	A	—	—	—	+	Alk	A	—	A	A	A	—	—	Del	—	—	—
49	1	A	A	—	—	—	—	Alk	—	—	—	A	A	—	—	—	—	—	A
51	1	A	A	—	—	—	—	A	—	—	—	A	A	A	A	—	—	—	—
55	1	A	A	—	—	—	+	Alk	A	A	A	A	A	A	—	—	—	—	—
56	1	A	A	—	—	—	—	A & C	—	—	A	A	A	A	A	—	—	—	—
64	1	A	A	—	—	—	+	Alk	A	—	A	A	A	A	—	—	—	—	—
65	1	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
67	1	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
68	4	A	A	—	—	—	+	Alk	A	—	A	A	A	A	A	—	—	—	—
69	1	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
70	1	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
74	6	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
75	9	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
76	1	A	A	—	—	—	+	Alk	A	—	A	A	A	A	—	—	—	—	—
78	7	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
79	2	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
86	1	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
91	1	A	A	—	—	—	+	A	—	—	—	A	A	—	—	—	—	—	—

Even in the primary series of tests, those dealing with the production of indol and the action of the bacilli on milk show very considerable discrepancies.

Unfortunately, as mentioned above, the exact method used for testing for indol is unknown, and some of the variations may be due to impurities of chemicals or media, &c., or to the method employed. As regards milk cultures it is well recognized that if such an unstable body is used as a culture medium aberrant results will occur.

When the results obtained by using the so-called secondary series of tests are examined, it is very clearly demonstrated that biochemical reactions are without any practical use in arranging bacilli in subgroups.

In Tables II, III, IV, and V the results of the primary and secondary tests obtained with a series of Flexner-Y bacilli, isolated from one particular case on a certain date, are given, and it is at once clear that even these results show many remarkable differences.

TABLE II

No. of Case	No. of Strain	Primary Series: Glucose	Mannite	Dulcite	Saccharose	Salicin	Indol	Milk—14 days	Secondary Series: Sorbite	Rhamnose	Maltose	Levulose	Galactose	Mannose	Raffinose	Dextrin	Inulin	Adonite	Glycerin
10	1	A	A	—	—	—	—	Alk	—	—	—	A	A	—	A	—	—	A	—
	2	A	A	—	—	—	—	Alk.AC	—	—	—	A	A	—	A	—	—	A	—
	3	A	A	—	—	—	+	AC	—	—	A	A	A	—	A	—	—	A	—
	4	A	A	—	—	—	—	Alk.AC	—	—	—	A	A	—	A	—	—	A	—
	5	A	A	—	—	—	+	Alk	—	—	A	A	A	—	A	—	—	A	—
	6	A	A	—	—	—	+	Alk.AC	—	—	—	A	A	—	A	—	—	A	—
	7	A	A	—	—	—	—	Alk	—	—	A	A	A	A	A	A	—	—	—
	8	A	A	—	—	—	+	Alk.AC	—	—	A	A	A	—	A	—	—	A	—

TABLE III

No. of Case	No. of Strain	Primary Series: Glucose	Mannite	Dulcite	Saccharose	Salicin	Indol	Milk—14 days	Secondary Series: Sorbite	Rhamnose	Maltose	Levulose	Galactose	Mannose	Raffinose	Dextrin	Inulin	Adonite	Glycerin
55	1	A	A	—	—	—	+	Alk	A	A	A	A	A	A	—	—	—	—	—
	2	A	A	—	—	—	+	Alk	A	A	—	A	A	A	—	—	—	—	—
	3	A	A	—	—	—	+	Alk	A	A	—	A	A	A	—	—	—	—	—
	4	A	A	—	—	—	+	Alk	A	A	A	A	A	A	—	—	—	—	—
	5	A	A	—	—	—	+	Alk	A	A	A	A	A	A	—	—	—	—	—
	6	A	A	—	—	—	+	Alk	A	A	—	A	A	A	—	—	—	—	—
	7	A	A	—	—	—	+	Alk	A	A	—	A	A	A	—	—	—	—	—
	8	A	A	—	—	—	+	Alk	A	—	A	A	A	A	—	—	—	—	—
	9	A	A	—	—	—	—	Alk	—	—	A	A	A	A	A	—	—	—	—

TABLE IV

No. of Case	No. of Strain	Primary Series: Glucose	Mannite	Dulcite	Saccharose	Salicin	Indol	Milk—14 days	Secondary Series: Sorbite	Rhamnose	Maltose	Levulose	Galactose	Mannose	Raffinose	Dextrin	Inulin	Adonite	Glycerin
65	1	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	2	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	5	A	A	—	—	—	+	Alk	A	A	A	A	A	A	—	A	—	—	A
	6	A	A	—	—	—	+	Alk	A	—	A	A	A	A	—	Del	—	—	—
	7	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	8	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—

TABLE V

No. of Case	No. of Strain	Primary Series: Glucose	Mannite	Dulcite	Saccharose	Salicin	Indol	Milk—14 days	Secondary Series: Sorbite	Rhamnose	Maltose	Levulose	Galactose	Mannose	Raffinose	Dextrin	Inulin	Adonite	Glycerin
68	4	A	A	—	—	—	+	Alk	A	—	A	A	A	A	A	—	—	—	—
	5	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—

In a former paper [1] Dr. Gettings pointed out that these variations of biochemical reactions were probably due to a different physiological action of the actual bacilli. The carbohydrate which was specially selected for this investigation was maltose, owing to its having been frequently stated that the true Flexner group could be separated from the Y group of bacilli by their respective actions on this sugar. The above conclusion was arrived at after an extended series of experiments, in which pure cultures of some of the strains were planted out on to plates of MacConkey's neutral red bile salt agar, to which maltose had been added in place of the lactose. Such a plate yielded colonies of two types, one of which was coloured red owing to its power of fermenting maltose; the other remained colourless, as the bacilli which gave rise to them were unable to ferment this sugar. Sub-cultures made from such colonies preserved these reactions, at any rate, for a time.

The full details of the biochemical reactions of the 285 strains isolated from 39 cases are given in Appendix I.

IV. Reactions with Specific Immune Sera.

1. *Is it possible to divide the members of the Flexner-Y group of dysentery bacilli into a number of sub-groups by means of the agglutination of emulsions of the different strains of bacilli by sera prepared through the medium of a single strain?*

Two specific agglutinating sera were prepared by inoculating rabbits with a series of doses of a vaccine prepared in the one case from the bacillus, Case 10, Strain 1, and in the other, Case 86, Strain 1—the first of these doses was given subcutaneously but the later ones intravenously.

The titre of these sera seemed to have varied considerably at different dates, and in the following table some of the figures found in the note-books are given. Although it cannot be stated absolutely, it is probable that fresh sera were prepared with both strains about May and June 1917.

TABLE VI

Serum prepared from Case 10, Strain 1		Serum prepared from Case 86, Strain 1	
Date	Titre	Date	Titre
9.6.14	3200 +	9.6.14	1600 + 3200 P
10.7.14	6400 +	9.7.14	6400 +
18.8.15	1600 + 3200 P	18.8.15	3200 + 6400 P
*14.6.17	4000 +	22.9.15	800 + 1600 P
30.6.17	1000 + 2000—	2.10.15	1000 + 3200 P
25.7.17	1000 + 2000—	9.10.15	800 + 1600 P
		*14.6.17	2000 + 4000 P
		30.6.17	1000 + 2000—

* At this date most probably freshly prepared sera were employed.

In this table and also in the following one + indicates complete agglutination; —, the absence of agglutination, P, partial agglutination, T. S., type strain.

[1] *Transact. Trop. Soc. Med. and Hyg.*, 1915, vol. vi.

TABLE

BACILLUS USED IN THE PREPARATION OF THE SERUM. CASE 10, STRAIN 1

Date of Experiment	9.6.14		10.7.14					2.10.15		20.10.15		9.10.15					20.6.17		Strain
Dilution of Serum	1 in 400	1 in 800	1 in 400	1 in 800	1 in 1600	1 in 3200	1 in 6400	1 in 400	1 in 800	1 in 400	1 in 800	1 in 50	1 in 100	1 in 200	1 in 400	1 in 800	1 in 500	1 in 1000	Case and with which agreement is shown by absorption test
No. of Case and Strain tested																			
Case 10 Strain 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	T. S.
1 5	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
6 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
7 1	+	+	...	...	...	...	...	+	+	+	+	...	...	...	...	...	...	...	10 1
8 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
9 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
11 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
17 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	..	...	...	10 1
19 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
22 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
23 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
24 1	+	+	+	+	+	+	+	—	—	+	+	...	...	...	...	...	...	...	10 1
26 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
28 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
38 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	..	...	...	10 1
39 1	...	...	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
40 1	+	+	+	+	P	—	—	—	—	—	—	+	+	+	+	+	—	—	170 1
47 1	—	—	...	...	...	...	...	—	—	+	+	+	+	+	+	+	...	...	— —
48 1	...	...	...	...	...	...	...	—	—	—	—	+	+	+	P	—	...	...	86 1
49 1	+	+	+	+	+	+	+	..	...	...	...	...	...	...	...	...	...	...	10 1
50 1	+	+	...	...	...	...	...	...	...	...	...	...	...	...	...	...	..	...	10 1
51 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
55 1	...	...	...	...	...	...	...	—	—	—	—	+	+	P	—	—	...	...	86 1
56 1	+	—	...	...	...	...	...	+	+	+	+	+	+	+	+	+	...	...	10 1
64 1	...	...	...	...	...	...	...	—	—	+	+	+	+	+	—	—	...	...	86 1
65 1	...	...	...	...	...	...	...	—	—	+	+	...	...	...	...	..	...	...	86 1
67 1	...	...	...	...	...	...	...	—	—	...	...	...	...	...	...	...	...	...	10 1
68 1	...	..	...	...	...	...	...	—	—	...	...	...	...	...	...	...	...	...	86 1
69 1	...	...	...	...	...	...	...	—	—	...	...	...	...	...	...	...	...	...	86 1

Throughout these experiments the following technique was employed:

The emulsions were made by suspending in 0·85 per cent. salt solution enough bacilli from an agar culture of eighteen to twenty-four hours to make a conveniently thin emulsion.

Usually only two dilutions of serum were employed, these were made in bulk, and in some of the experiments were considerably below the full titre of the serum.

The tests were carried out in small test-tubes ($4 \times \frac{3}{8}$ inch), and equal volumes of the emulsions and dilutions of serum were mixed in these. When a series of tubes had been filled in they were placed in a water-bath. In the earlier experiments a temperature of 37° C. was employed, while later 45° C. was at times used. Readings were made after the tubes had been in the water-bath from two to four hours; after this reading the tubes were removed from the water-bath and kept on the bench until the following morning, when a confirmatory reading was made.

VII

BACILLUS USED IN THE PREPARATION OF THE SERUM. CASE 86, STRAIN 1

Date of Experiment		10.6.14		10.7.14					28.10.14		6.9.15		9.10 15					20.6.17	
Dilution of Serum		1 in 400	1 in 800	1 in 400	1 in 800	1 in 1600	1 in 3200	1 in 6400	1 in 400	1 in 800	1 in 400	1 in 800	1 in 50	1 in 100	1 in 200	1 in 400	1 in 800	1 in 500	1 in 1000
No. of Case and Strain tested																			
Case 10	Strain 1	—	—	...	...	...	...	...	+	+	—	—							
1	5	—	—	...	...	...	...	...	+	+	—	—							
6	1	—	—	...	...	...	...	...	+	—	—	—							
7	1	—	—	...	...	...	...	...	+	+	—	—							
8	1	—	—	...	...	...	...	...	+	+	—	—							
9	1	—	—	...	...	...	...	...	+	+	P	P							
11	1	—	—	...	...	...	...	...	+	+	P	P							
17	1	—	—	...	...	...	...	...	+	+	—	—							
19	1	—	—	...	...	...	...	...	+	+	P	P							
22	1	—	—	...	...	...	...	...	+	+	—	—							
23	1	—	—	...	...	...	...	...	+	+	—	—							
24	1	—	—	...	...	...	...	...	+	+	—	—							
26	1	—	—	...	...	...	...	...	+	+	—	—							
28	1	—	—	...	...	...	...	...	+	+	—	—							
38	1	—	—	...	...	...	...	...	+	+	P	P							
39	1	—	—	...	...	...	...	...	+	+	—	—							
40	1	—	—	...	...	...	...	...	—	—	—	—	...	...	...	...	...	—	—
47	1	—	—	...	...	...	...	...	+	+	P	P	+	+	P	—	—		
48	1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
49	1	—	—	...	...	...	...	...	+	+	P	P							
50	1	—	—	...	...	...	...	...	+	+	—	—							
51	1	—	—	...	...	...	...	...	+	+	P	P							
55	1	+	+	+	+	+	+	+	+	+	+	+							
56	1	—	—	...	...	...	...	...	+	+	—	—	+	P	—	—	—		
64	1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
65	1	+	+	+	+	+	+	+	+	+	+	+							
67	1	+	+	+	+	+	+	+	+	+									
68	1	+	+	+	+	+	+	+	+	+	+	+							
69	1	+	+	+	+	+	+	+	+	+	+	+							

Salt solution controls were employed with every emulsion, and frequently, when discordant results were obtained, a series of tubes, in which were placed dilutions of normal rabbit's serum, were employed as a control.

In the following table the results obtained with the strains selected from the first twenty-nine cases are given; these are sufficient to show how much overlapping there was in the results.

A full record of the results of the agglutination tests obtained with two sera mentioned above and a selected strain from ninety-nine different cases is given in Appendix II. To these have been added, whenever the data could be given, the results obtained by means of absorption tests which are described in the last portion of the paper.

To sum up the conclusion drawn from these experiments, it may be stated that although these results were much more encouraging than those obtained from the study of the biochemical reactions they were not sufficiently sharp or constant to enable definite sub-

groups to be made. However, they strongly supported the supposition that the Flexner-Y group of dysentery bacilli did consist of a number of sub-groups which were very nearly related to one another. It may here be noted that on several occasions various sera, including both those prepared by means of a single strain, and others prepared by means of several strains of this group of bacilli, were tested to ascertain if they had any power to agglutinate bacilli not belonging to this group such as *B. typhosus* and *B. dysenteriae*, Shiga; these experiments gave uniformly negative results.

2. *Is it possible to divide the members of the Flexner-Y group of bacilli into a number of sub-groups by means of the absorption of the specific 'agglutinins' by the different strains of bacilli from sera prepared through the medium of a single strain?*

The technique employed in carrying out the absorption tests was as follows: the bacillus to be tested was planted out on agar slopes which were then incubated for eighteen to twenty-four hours at 37° C. After removing any water of condensation that might have collected, the growth was washed off the slope with a minimum of salt solution, usually about 1 c.c.; if this emulsion was not thick enough, it was added to another agar culture and the growth from this second tube was then washed off with it. When a sufficiently thick emulsion had been prepared, a measured quantity was added to a measured quantity of the serum; usually $1\frac{1}{2}$ to 2 c.c. of the emulsion were added to $1\frac{1}{2}$ to 2 c.c. of a 1 in 10 dilution of the serum. This mixture was made in a small test-tube which was placed either in a water-bath or the incubator at 37° C. for from two to four hours, and then kept at laboratory temperature overnight.

It was found out by experiment that in order to remove all the agglutinins from a 1 in 20 dilution of one of the immune sera employed in these tests, it was necessary to add the growth from two agar slopes. With smaller quantities, for instance, the growth from one agar slope, the agglutinins were only partially removed. This serum had an agglutination titre of 1 in 1500. In order to avoid errors, throughout the tests, sufficient bacilli were always added to remove *all* the agglutinins from the dilution of the serum employed.

In the following table the degree of agglutinating power remaining after a 1 in 20 dilution of a serum had been treated with varying quantities of the homologous bacillus is shown.

TABLE VIII

Serum tested	Dilutions of Serum							
	1 in 40	1 in 80	1 in 160	1 in 320	1 in 640	1 in 1280	1 in 1500	1 in 2000
Untreated	+	+	+	+	+	+	+	—
Absorbed with one loopful of bacilli	+	+	+	+	P	—	—	—
Absorbed with one loopful of bacilli	+	+	+	+	—	—	—	—
Absorbed with two loopfuls of bacilli	+	+	+	P	—	—	—	—
Absorbed with three loopfuls of bacilli	+	+	+	P	—	—	—	—
Absorbed with bacilli from ½ an agar slope	+	+	P	—	—	—	—	—
Absorbed with bacilli from 1 agar slope	+	+	—	—	—	—	—	—
Absorbed with bacilli from 2 agar slopes	—	—	—	—	—	—	—	—

The sign + indicates that when the serum either had been absorbed with the quantity of bacilli mentioned or had not been treated, agglutination of an ordinary thin emulsion took place in that dilution.
P indicates partial agglutination.
— indicates that no agglutination took place.

The next day the tubes containing the mixtures of thick emulsion and serum were centrifuged until the supernatant fluid was quite clear; this was pipetted off, and dilutions such as 1 in 40, 1 in 80, 1 in 160, &c., having been made, two series of tubes were filled in with equal quantities of these dilutions and thin emulsions of (i) the bacillus used in absorbing the serum, (ii) the bacillus used in the preparation of the serum. If the serum was found to have lost all power of agglutinating both the bacillus used in absorbing the serum and also the bacillus used in the preparation of the serum, the two bacilli belonged to the same sub-group; if, however, it was found that the serum had the power of agglutinating the bacillus used in the preparation of the serum, although it had completely lost the power to agglutinate emulsions of the bacillus used in absorbing the serum, it belonged to another sub-group.

Using this technique a number of strains of the Flexner-Y group were tested, one strain from each case being investigated. As the strains were placed in different sub-groups it was found that there were some which could not be allocated by means of the sera available; it was therefore necessary to prepare other sera, and in all five sera were employed, with the result that all the strains, 87 in number, were found to correspond with one or other of the strains used in preparing these five sera, with the exception of three. The results obtained by this technique were perfectly sharply defined, and no matter how often the experiments were repeated the results were always exactly the same.

Leaving out one small group consisting of only two strains, which will be discussed later, four definite sub-groups of the Flexner-Y group of bacilli were identified.

Sub-group 1, in which Case 10, Strain 1, was used in preparing the serum, consisted, in all, of forty members.

Sub-group 2, in which Case 86, Strain 1, was used in preparing the serum, consisted, in all, of thirty members.

Sub-group 3, in which Case 170, Strain 1, was used in preparing the serum, consisted, in all, of eleven members.

Sub-group 4, in which Case 311, Strain 1, was used in preparing the serum, consisted, in all, of eleven members.

In other words, of the 92 strains tested, 43·5 per cent. belonged to Sub-group 1, 32·6 belonged to Sub-group 2, 12 per cent. to Sub-group 3, and 12 per cent. to Sub-group 4. The three remaining strains could not be placed in any of these sub-groups.

In the following tables are shown the sub-groups to which each strain belongs as far as they have been worked out. These are also given in Table VII, in the text, and Tables 1, 2, 3, 4, and 5, Appendix II.

TABLE IX

No. of Case and Strain showing agreement with Case 10, Strain 1, by absorption test

Case	Strain	Case	Strain	Case	Strain	Case	Strain	Case	Strain
1	5	22	1	50	?	130	1	307	2
6	1	23	1	51	1	131	1	318	1
7	1	24	1	56	1	136	1	319	1
8	1	26	1	67	1	139	1	321	1
9	1	28	1	91	1	154	1	322	1
11	1	38	1	92	10	168	1	325	1
17	1	39	1	100	1	169	1	336	?
19	1	49	1	113	1	269	1		

TABLE X

No. of Case and Strain showing agreement with Case 86, Strain 1, by absorption test

Case	Strain	Case	Strain	Case	Strain	Case	Strain	Case	Strain
48	1	70	1	126	1	149	1	221	2
55	1	74	6	128	1	176	1	222	2
64	1	75	9	137	1	178	1	271	5
65	1	76	1	141	1	185	1	291	1
68	4	78	7	144	1	189	1	326	2
69	1	79	2	148	1	196	1		

TABLE XI

No. of Case and Strain showing agreement with Case 170, Strain 1, by absorption test

Case	Strain	Case	Strain	Case	Strain	Case	Strain	Case	Strain
40	1	156	1	159	3	164	1	167	1
79a	4	157	1	161	1	165	1	184	1

TABLE XII

No. of Case and Strain showing agreement with Case 311, Strain 1, by absorption test

Case	Strain	Case	Strain	Case	Strain	Case	Strain	Case	Strain
126*a*	?	200	1	225	1	260	3	270	1
172	1	219	2	231	?	268	1	290	1

As regards Case 275, Strain 2, one strain, namely Case 252, Strain 1, was found to be in complete agreement with it by the absorption test. On investigating these cultures further the bacilli were found to be motile, no indol was produced by either culture, and their growth in litmus milk produced no change in that medium. Emulsions of Case 275, Strain 2, were on several occasions put up with dilutions of an antityphoid agglutinating serum obtained from the Lister Institute, but no definite agglutination was ever recorded even when comparatively low dilutions were employed. A serum, however, prepared by inoculating a rabbit with a vaccine prepared from this bacillus (Case 275, Strain 2) agglutinated emulsions of stock typhoid cultures, and of the bacillus in question, to exactly the same titre ; further absorption tests both with the Lister Institute typhoid agglutinating serum and the serum prepared by means of the bacillus Case 275, Strain 2, demonstrated that this bacillus and also that isolated from Case 252, Strain 1, were undoubted typical *B. typhosus*, which were evidently unaffected as regards agglutination by the high titre (1 in 6,000) typhoid agglutinating serum obtained from the Lister Institute.

From agglutination tests the sub-group agreeing with Case 170, Strain 1, appears to be identical with the 'Oxford'-Y strain, but this cannot be stated definitely as the agglutination tests were not performed with full-titre dilutions of the serum, and no record of any absorption tests can be found.

V. Summary and Conclusions

(1) From the first part of the paper, in which the biochemical reactions are studied, the following conclusions may be drawn; that, although the biochemical reactions with a certain small selected number of carbohydrates are, as is usually recognized, extremely useful as a *rough* means of identification of members of the coliform group of bacilli, it is quite futile to attempt to classify a group of very nearly related bacilli, such as the Flexner-Y group of dysentery bacilli, into definite sub-groups by using an extended series of these carbohydrates such as the 'secondary series' introduced by Lewis.

Even the use of maltose as a means for distinguishing the Y type of dysentery bacilli from the typical Flexner type was shown to give fallacious results.

(2) In the second portion of the paper dealing with ordinary agglutination tests it was shown, without in any way detracting from the value of such tests for definitely recognizing the various

bacteria of the coliform group of bacilli, that it was not feasible to divide by such means the Flexner-Y group of dysentery bacilli into a number of sharply defined sub-groups, the results obtained being neither sufficiently sharp nor constant. These tests, however, when they were carried out with sera prepared through the medium of a single strain, strongly confirmed the supposition that the Flexner-Y group of dysentery bacilli did consist of a number of sub-groups, the members of which were very nearly related to one another.

(3) In the last portion of the paper, which was unfortunately not quite, though very nearly, completed, the tests in which the different strains of the Flexner-Y group were identified by means of the absorption of the agglutinins from specific sera gave both very sharp and very constant results, and by the data thus arrived at it was possible to place 92 out of the 95 strains of the Flexner-Y group of dysentery bacilli that were investigated into four sub-groups.

Sub-group 1 consisted of forty members, that is 43·5 per cent.
Sub-group 2 consisted of thirty members, that is 32·6 per cent.
Sub-group 3 consisted of eleven members, that is 12 per cent.
Sub-group 4 consisted of eleven members, that is 12 per cent.

The remaining three strains could not be placed in any of the above, so that there is at least one other sub-group unidentified.

Certain evidence which, however, is not conclusive points to Sub-group 3 being identical with that usually called the Y group of dysentery bacilli.

APPENDIX I

In Appendix I the details of the biochemical reactions of 285 strains of the Flexner-Y group of bacilli isolated from thirty-nine cases are recorded.

Throughout these tables the following symbols and abbreviations are employed :

A indicates the fermentation of a certain carbohydrate with the production of acid, or that acid was produced in a milk culture.

A.s and A.v.s indicates that the production of acid was slight or very slight.

+ indicates that indol was produced after the bacillus had been growing in peptone water for seven days.

— indicates that no fermentation of the carbohydrate in question occurred, or that no indol was produced in a peptone water culture.

Alk indicates that the milk culture was rendered more alkaline.

A & C indicates that acid and clot were both produced in the milk culture.

Dcl indicates that the litmus used as an indicator was decolorized.

DETAILS OF BIOCHEMICAL REACTIONS OF VARIOUS CASES

		Primary Series							Secondary Series										
No. of Case	No. of Strain	Glucose	Mannite	Dulcite	Saccharose	Salicin	Indol	Milk—14 days	Sorbite	Rhamnose	Maltose	Levulose	Galactose	Mannose	Raffinose	Dextrin	Inulin	Adonite	Glycerin
1	2	A	A	—	—	—	+	A	—	—	—	A	A	A	A	—	—	—	—
	3	A	A	—	—	—	—	A	—	—	—	A	A	A	A	—	—	—	—
	4	A	A	—	—	—	—	A	—	—	—	A	A	A	A.s	—	A.s	—	—
	5	A	A	—	—	—	—	A	—	—	—	A	A	A	A.s	—	—	—	—
	6	A	A	—	—	—	—	A	—	—	—	A	A	A	A.s	—	—	—	—
	7	A	A	—	—	—	—	A	—	—	A.s	A	A	A	A	—	—	—	—
6		A	A	—	—	—	—	A	—	—	A.s	A	A	A	A	A.s	—	—	—
	2	A	A	—	—	—	—	A	A.s	—	A	A	A	A	A	A	A	—	—
	3	A	A	—	—	—	—	A	—	—	A.s	A	A	A	A	A.s	A.s	—	—
	4	A	A	—	—	—	—	A	A	—	A	A	A	A	A	A.s	A.s	—	—
	5	A	A	—	—	—	—	A	—	—	A	A	A	A	A	A.s	A.s	—	—
	6	A	A	—	—	—	—	A	—	—	A.s	A	A	A	A	A.s	A.s	—	—
	7	A	A	—	—	—	—	A	—	—	A.s	A	A	A	A	A	A.s	—	A
	8	A	A	—	—	—	—	A	A.s	—	A	A	A	A	A	A	A.s	—	—
	9	A	A	—	—	—	—	A	—	—	A	A	A	A	A	A	A.s	—	—
	10	A	A	—	—	—	—	A	—	—	A	A	A	A	A	A	A.s	—	—
7	1	A	A	—	—	—	—	A	—	—	A	A	A	A	A	—	—	—	—
	2	A	A	—	—	—	—	A	—	—	—	A	A	A	A	—	—	—	—
	3	A	A	—	—	—	—	A	—	—	—	A	A	A	A	—	—	—	—
	4	A	A	—	—	—	—	A	—	—	—	A	A	A	A	—	—	—	—
	5	A	A	—	—	—	—	A	—	—	—	A	A	A	A	—	—	—	—
	6	A	A	—	—	—	—	A	—	—	—	A	A	A	A	—	—	—	—
	7	A	A	—	—	—	—	A	A	—	A	A	A	A	A	A	—	A	—
	8	A	A	—	—	—	+	A	—	—	A	A	A	A	A	—	—	—	—
	9	A	A	—	A.v.s	—	—	A	—	—	A	A	A	A	A	—	—	—	—
	10	A	A	—	—	—	—	A	—	—	A	A	A	A	A	—	—	—	—

		Primary Series								Secondary Series										
No. of Case	No. of Strain	Glucose	Mannite	Dulcite	Saccharose	Salicin	Indol	Milk—14 days		Sorbite	Rhamnose	Maltose	Levulose	Galactose	Mannose	Raffinose	Dextrin	Inulin	Adonite	Glycerin
8	1	A	A	—	—	—	—	A		—	—	A	A	A	A	A	A	—	—	—
	2	A	A	—	—	—	—	A		—	—	—	A	A	A	A	—	—	—	—
9	1	A	A	—	—	—	+	Alk		—	—	A	A	A	A	A	A	—	—	—
	2	A	A	—	—	—	—	Alk		—	—	A	A	A	A	A	A	—	—	—
	3	A	A	—	—	—	—	Alk		—	—	A	A	A	A	A	A	—	—	—
	4	A	A	—	—	—	+	Alk		—	—	A	A	A	A	A	A	—	—	—
	5	A	A	—	—	—	+	Alk		—	—	A	A	A	A	A	A	—	—	—
	6	A	A	—	—	—	+	Alk		—	—	A	A	A	A	A	A	—	A	—
	7	A	A	—	—	—	+	Alk		—	—	A	A	A	A	A	A	—	A	—
	8	A	A	—	—	—	+	Alk		—	—	A	A	A	A	A	A	—	—	—
	9	—	A	—	—	—	—	Alk		—	—	A	A	A	A	A	A	A	—	—
	10	A	A	—	—	—	+	Alk		—	—	A	A	A	A	A	A	—	—	—
10	1	A	A	—	—	—	—	Alk		—	—	—	A	A	—	A	—	—	A	—
	2	A	A	—	—	—	—	Alk		—	—	—	A	A	—	A	—	—	A	—
	3	A	A	—	—	—	+	Alk		—	—	A	A	A	—	A	—	—	A	—
	4	A	A	—	—	—	—	Alk		—	—	—	A	A	—	A	—	—	A	—
	5	A	A	—	—	—	+	Alk		—	—	A	A	A	—	A	—	—	A	—
	6	A	A	—	—	—	+	Alk		—	—	—	A	A	—	A	—	—	A	—
	7	A	A	—	—	—	—	Alk		—	—	A	A	A	A	A	A	—	—	—
	8	A	A	—	—	—	+	Alk		—	—	A	A	A	—	A	—	—	A	—
11	1	A	A	—	—	—	+	Alk		—	—	—	A	A	—	A	—	—	A	—
	2	A	A	—	—	—	+	Alk		—	—	A	A	A	—	A	—	—	A	—
	3	A	A	—	—	—	—	Alk		—	—	—	A	A	—	A	—	—	A	—
	4	A	A	—	—	—	—	Alk		—	—	—	A	A	A	A	—	—	A	—
	5	A	A	—	—	—	+	Alk		—	—	—	A	A	—	A	—	—	A	—
	6	A	A	—	—	—	—	Alk		—	—	—	A	A	—	A	—	—	A	—
	7	A	A	—	—	A	+	Alk		—	—	—	A	A	—	A	—	—	A	—
	8	A	A	—	—	—	+	Alk		—	—	—	A	A	—	A	—	—	A	—
	9	A	A	—	—	—	+	Alk		—	—	—	A	A	—	A	—	—	A	—
	10	A	A	—	—	—	—	Alk		—	—	—	A	A	—	A	—	—	A	—
14	1	A	A	—	—	—	—	Alk		—	—	—	A	A	—	A	—	—	A	—
	2	A	A	—	—	—	—	Alk		—	—	—	A	A	—	A	—	—	A	—
	4	A	A	—	—	—	—	Alk		—	—	A	A	A	—	A	—	—	A	—
	5	A	A	—	—	—	—	Alk		—	—	A	A	A	—	A	—	—	A	—
	6	A	A	—	—	—	—	Alk		—	—	—	A	A	—	A	—	—	A	—
	10	A	A	—	—	—	—	A		—	—	—	A	A	—	A	—	—	A	—
17	1	A	A	—	—	—	—	Alk		—	—	—	A	A	A	A	—	—	—	—
	2	A	A	—	—	—	—	Alk		—	—	—	A	A	A	Del	—	—	—	—
	3	A	A	—	—	—	—	Alk		—	—	—	A	A	A	—	—	—	—	—
	4	A	A	—	—	—	—	Alk		—	—	—	A	A	A	—	—	—	—	—
	5	A	A	—	—	—	—	Alk		—	—	—	A	A	A	Del	—	—	—	—
	6	A	A	—	—	—	+	Alk		—	—	—	A	A	A	A	—	—	—	—
	7	A	A	—	—	—	—	Alk		—	—	—	A	A	A	A	—	—	—	—
	8	A	A	—	—	—	—	Alk		—	—	A	A	A	A	A	—	—	—	—
	9	A	A	—	—	—	—	Alk		—	—	A	A	A	A	A	—	—	—	—
	10	A	A	—	—	—	+	Alk		—	—	—	A	A	A	A	—	—	—	—

		Primary Series							Secondary Series										
No. of Case	No. of Strain	Glucose	Mannite	Dulcite	Saccharose	Salicin	Indol	Milk—14 days	Sorbite	Rhamnose	Maltose	Levulose	Galactose	Mannose	Raffinose	Dextrin	Inulin	Adonite	Glycerin
19	1	A	A	—	—	—	—	Alk	—	—	A	A	A	A	A	—	—	—	—
	2	A	A	—	—	—	—	A	—	—	A	A	A	A	—	—	—	—	—
	3	A	A	—	—	—	+ ?	A	—	—	A	A	A	A	A	Del	—	—	—
	4	A	A	—	—	—	—	A	—	—	—	A	A	A	—	—	—	—	—
	5	A	A	—	—	—	—	A	—	—	—	A	A	A	—	—	—	—	—
	6	A	A	—	—	—	—	Alk	—	—	A	A	A	A	—	—	—	—	—
	7	A	A	—	—	—	—	Alk	—	—	—	A	A	A	—	—	—	—	—
	8	A	A	—	—	—	—	Alk	—	—	—	A	A	A	A	—	—	—	—
	9	A	A	—	—	—	—	Alk	—	—	—	A	A	A	—	—	—	—	—
	10	A	A	—	—	—	—	Alk	—	—	—	A	A	A	—	—	—	—	—
22	1	A	A	—	—	—	—	Alk	—	—	A	A	A	A	—	—	—	—	—
	2	A	A	—	—	—	—	Alk	—	—	A	A	A	A	—	—	—	—	—
	3	A	A	—	—	—	—	Alk	—	—	—	A	A	A	—	—	—	—	—
23	1	A	A	—	—	A	—	A & C	—	—	—	A	A	A	A	—	—	—	—
	2	A	A	—	—	—	+	A & C	—	—	—	A	A	A	A	—	—	—	—
	3	A	A	—	—	—	—	Alk	—	—	A	A	A	A	A	—	—	—	—
	4	A	A	—	—	—	—	Alk	—	—	—	A	A	A	A	—	—	—	—
	5	A	A	—	—	—	—	Alk	—	—	—	A	A	A	A	—	—	—	—
	6	A	A	—	—	—	—	Alk	—	—	A	A	A	A	A	Del	—	—	—
	7	A	A	—	—	—	—	A & C	—	—	A	A	A	A	A	—	—	—	—
	8	A	A	—	—	—	—	Alk	—	—	—	A	A	A	A	—	—	—	—
	9	A	A	—	—	—	+	Alk	—	—	—	A	A	A	A	—	—	—	—
	10	A	A	—	—	—	—	Alk	—	—	—	A	A	A	A	—	—	—	—
24	1	A	A	—	—	—	+	Alk	—	—	A	A	A	A	A	Del	—	—	—
	2	A	A	—	—	—	+	Alk	—	—	A	A	A	A	A	A	—	—	—
	3	A	A	—	—	—	—	A & C	—	—	A	A	A	A	A	—	—	—	A
	4	A	A	—	—	—	+	A & C	—	—	A	A	A	A	A	—	—	—	—
	5	A	A	—	—	A	+	A & C	—	—	—	A	A	A	A	—	—	—	—
	6	A	A	—	—	—	—	Alk	—	—	A	A	A	A	A	A	—	—	—
	7	A	A	—	—	—	—	Alk	—	—	A	A	A	A	A	—	—	—	—
	8	A	A	—	—	—	—	Alk	—	—	A	A	A	A	A	A	—	—	—
	9	A	A	—	—	—	—	A & C	—	—	A	A	A	A	A	A	—	—	—
	10	A	A	—	—	—	+	A	—	—	A	A	A	A	A	—	—	—	—
26	1	A	A	—	—	—	+	Alk	—	—	A	A	A	A	—	—	—	—	—
	2	A	A	—	—	—	+	Alk	—	—	A	A	A	A	—	—	—	—	—
	3	A	A	—	—	—	+	Alk	—	—	A	A	A	A	—	—	—	—	—
	4	A	A	—	—	—	+	Alk	—	—	A	A	A	A	—	—	—	—	—
	5	A	A	—	—	—	+	Alk	—	—	A	A	A	A	—	—	—	—	—
	6	A	A	—	—	—	+	Alk	—	—	A	A	A	A	—	—	—	—	—
	7	A	A	—	—	—	+	Alk	—	—	A	A	A	A	—	—	—	—	—
	8	A	A	—	—	—	+	Alk	—	—	A	A	A	A	—	—	—	—	—
	9	A	A	—	—	—	+	Alk	—	—	A	A	A	A	—	—	—	—	—
	10	A	A	—	—	—	+	Alk	—	—	A	A	A	A	—	—	—	—	—
28	1	A	A	—	—	—	+	A	—	—	—	A	A	A	—	—	—	—	—
	4	A	A	—	—	—	+	A	—	—	A	A	A	A	—	—	—	A	—
	6	A	A	—	—	—	+	A	—	—	A	A	A	—	—	—	—	A	—

		Primary Series							Secondary Series										
No. of Case	No. of Strain	Glucose	Mannite	Dulcite	Saccharose	Salicin	Indol	Milk—14 days	Sorbite	Rhamnose	Maltose	Levulose	Galactose	Mannose	Raffinose	Dextrin	Inulin	Adonite	Glycerin
38	1	A	A	—	—	—	+	A	—	—	—	A	A	A	—	—	—	A	—
	2	A	A	—	—	—	+	A	—	—	—	A	A	A	A	—	—	A	—
	3	A	A	—	—	—	+	A	—	—	A	A	A	A	A	—	—	—	—
	4	A	A	—	—	—	+	A	—	—	—	A	A	A	A	—	—	—	—
	5	A	A	—	—	—	+	A	—	—	A	A	A	A	A	—	—	—	—
	6	A	A	—	—	—	+	A	—	—	A	A	A	A	—	—	—	A	—
	7	A	A	—	—	—	+	A	—	—	—	A	A	A	A	—	—	—	—
	8	A	A	—	—	—	+	A	—	—	—	A	A	A	A	—	—	A	—
	9	A	A	—	—	—	+	A	—	—	—	A	A	A	A	—	—	—	—
	10	A	A	—	—	—	+	A	—	—	—	A	A	A	—	—	—	A	—
39	1	A	A	—	—	—	+	A	—	—	A	A	A	—	—	—	—	A	—
	2	A	A	—	—	—	+	A	—	—	—	A	A	A	—	—	—	A	—
	3	A	A	—	—	—	+	A	—	—	—	A	A	—	—	—	—	A	—
	4	A	A	—	—	—	+	A	—	—	—	A	A	—	—	—	—	A	—
	5	A	A	—	—	—	+	A	—	—	—	A	A	—	—	—	—	A	—
	6	A	A	—	—	—	+	A	—	—	—	A	A	—	—	Del	—	A	—
	7	A	A	—	—	—	+	A	—	—	—	A	A	—	—	—	—	A	—
	8	A	A	—	—	—	+	A	—	—	A	A	A	—	—	—	—	A	—
	9	A	A	—	—	—	+	A	—	—	—	A	A	—	—	—	—	A	—
	10	A	A	—	—	—	+	A	—	—	—	A	A	—	—	—	—	A	—
40	1	A	A	—	—	—	+	A	A	—	A	A	A	—	—	—	—	A	—
	2	A	A	—	—	—	+	A	A	—	A	A	A	—	—	—	—	A	—
	3	A	A	—	—	—	+	A	A	—	A	A	A	—	—	—	—	A	—
	4	A	A	—	—	—	+	A	A	—	A	A	A	—	—	—	—	A	—
	5	A	A	—	—	—	+	A	Del	—	A	A	A	—	—	—	—	A	—
	9	A	A	—	—	—	+	A	A	—	A	A	A	—	—	—	—	A	—
	10	A	A	—	—	—	+	A	Del	—	A	A	A	—	—	—	—	A	—
47	1	A	A	—	—	—	—	Alk	—	—	—	A	A	A	A	—	—	—	—
	5	A	A	—	—	—	—	Alk	—	—	—	A	A	A	Del	—	—	—	—
	6	A	A	—	—	—	—	Alk	—	—	A	A	A	A	A	—	—	—	—
	7	A	A	—	—	—	—	A	—	—	—	A	A	A	A	—	—	A	—
	8	A	A	—	—	—	—	Alk	—	—	—	A	A	A	A	—	—	—	—
	9	A	A	—	Del	—	—	Alk	—	—	A	A	A	A	A	—	—	—	—
	10	A	A	—	—	—	—	Alk	—	—	—	A	A	A	A	—	—	—	—
48	1	A	A	—	—	—	+	Alk	A	—	A	A	A	—	—	Del	—	—	—
	2	A	A	—	—	—	+	Alk	A	A	A	A	A	A	—	Del	—	—	—
49	1	A	A	—	—	—	—	Alk	—	—	—	A	A	—	—	—	—	—	A
	2	A	A	—	—	—	—	Alk	—	—	—	A	A	A	Del	—	—	—	—
	3	A	A	—	—	—	—	Alk	—	—	—	A	A	A	—	—	—	—	—
	4	A	A	—	—	—	—	Alk	—	—	—	A	A	—	—	—	—	—	—
	5	A	A	—	—	—	—	Alk	—	—	—	A	A	A	A	—	—	—	—
	6	A	A	—	—	—	—	Alk	—	—	—	A	A	A	A	—	—	—	—
	7	A	A	—	—	—	—	Alk	—	—	—	A	A	A	A	—	—	—	—
	8	A	A	—	—	—	—	Alk	—	—	A	A	A	A	A	—	—	—	—

		Primary Series							Secondary Series										
No. of Case	No. of Strain	Glucose	Mannite	Dulcite	Saccharose	Salicin	Indol	Milk—14 days	Sorbite	Rhamnose	Maltose	Levulose	Galactose	Mannose	Raffinose	Dextrin	Inulin	Adonite	Glycerin
50	1	A	A	—	—	—	—	Alk	—	—	—	A	A	—	A	—	—	—	—
	2	A	A	—	—	—	—	Alk	—	—	—	A	A	A	A	—	—	—	—
	3	A	A	—	—	—	—	A	—	—	—	A	A	—	A	—	—	—	—
	4	A	A	—	—	—	—	A	—	—	—	A	A	—	A	—	—	—	—
	5	A	A	—	—	—	—	A	—	—	—	A	A	A	A	—	—	—	—
	6	A	A	—	—	—	—	A	—	—	—	A	A	—	A	—	—	—	—
	7	A	A	—	—	—	—	A	—	—	—	A	A	A	A	—	—	—	—
	8	A	A	—	—	—	—	A	—	—	—	A	A	—	A	—	—	A	—
	9	A	A	—	—	—	—	A	—	—	—	A	A	—	A	—	—	A	—
	10	A	A	—	—	—	—	A	—	—	—	A	A	—	A	—	—	—	—
51	1	A	A	—	—	—	—	A	—	—	—	A	A	A	A	—	—	—	—
	2	A	A	—	—	—	—	A	—	—	—	A	A	A	A	—	—	—	—
	3	A	A	—	—	—	—	A	—	—	—	A	A	A	A	—	—	—	—
	4	A	A	—	—	—	—	A	—	—	—	A	A	A	A	—	—	—	—
	5	A	A	—	—	—	—	A	—	—	—	A	A	A	A	—	—	—	—
	6	A	A	—	—	—	+	A	—	—	—	A	A	A	A	—	—	—	—
	7	A	A	—	—	—	—	A	—	—	—	A	A	A	A	—	—	—	—
	8	A	A	—	—	—	—	A	—	—	—	A	A	A	A	—	—	—	—
	9	A	A	—	—	—	—	A & C	—	—	—	A	A	A	A	—	—	—	—
55	1	A	A	—	—	—	+	Alk	A	A	A	A	A	A	—	—	—	—	—
	2	A	A	—	—	—	+	Alk	A	A	—	A	A	A	—	—	—	—	—
	3	A	A	—	—	—	+	Alk	A	A	—	A	A	A	—	—	—	—	—
	4	A	A	—	—	—	+	Alk	A	A	A	A	A	A	—	—	—	—	—
	5	A	A	—	—	—	+	Alk	A	A	A	A	A	A	—	—	—	—	—
	6	A	A	—	—	—	+	Alk	A	A	—	A	A	A	—	—	—	—	—
	7	A	A	—	—	—	+	Alk	A	A	—	A	A	A	—	—	—	—	—
	8	A	A	—	—	—	+	Alk	A	—	A	A	A	A	—	—	—	—	—
	9	A	A	—	—	—	—	Alk	—	—	A	A	A	A	A	—	—	—	—
56	1	A	A	—	—	—	—	A & A C	—	—	A	A	A	A	A	—	—	—	—
64	1	A	A	—	—	—	+	Alk	A	—	A	A	A	A	—	—	—	—	—
	2	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	3	A	A	—	—	—	+	Alk	A	—	A	A	A	A	—	—	—	—	—
	4	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	5	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	6	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	7	A	A	—	—	—	+	Alk	A	—	—	A	A	—	—	—	—	—	—
	8	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	9	A	A	—	—	—	+	Alk	A	A	—	A	A	A	—	—	—	—	—
	10	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
65	1	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	2	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	5	A	A	—	—	—	+	Alk	A	A	A	A	A	A	—	A	—	—	A
	6	A	A	—	—	—	+	Alk	A	—	A	A	A	A	—	Del	—	—	—
	7	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	8	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
67	1	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	2	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	3	A	A	—	—	—	+	Alk	A	—	A	A	A	—	—	—	—	—	—
	4	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	6	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	8	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	9	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	10	A	A	—	—	—	+	Alk	A	—	A	A	A	A	—	—	—	—	—

		Primary Series							Secondary Series										
No. of Case	No. of Strain	Glucose	Mannite	Dulcite	Saccharose	Salicin	Indol	Milk—14 days	Sorbite	Rhamnose	Maltose	Levulose	Gelactose	Mannose	Raffinose	Dextrin	Inulin	Adonite	Glycerin
68	4	A	A	—	—	—	+	Alk	A	—	A	A	A	A	A	—	—	—	—
	5	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
69	1	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	2	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	4	A	A	—	—	—	+	Alk	A	A	—	A	A	A	—	—	—	—	—
	5	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	6	A	A	—	—	—	+	Alk	A	A	—	A	A	A	—	—	—	—	—
70	1	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
	6	A	A	—	—	—	+	Alk	—	—	A	A	A	A	—	—	—	—	—
74	1	A	A	—	—	—	+	Alk	—	A	—	A	A	A	—	—	—	—	—
	2	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
	3	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	A	—	—	—
	4	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	6	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	8	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	9	A	A	—	—	—	+	Alk	A	A	—	A	A	A	—	—	—	—	—
	10	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
75	1	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
	2	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
	3	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
	4	A	A	—	—	—	+	Alk	—	A	—	A	A	A	—	—	—	—	—
	5	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
	6	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
	7	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
	9	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
	10	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
76	1	A	A	—	—	—	+	Alk	A	—	A	A	A	A	—	—	—	—	—
	2	A	A	—	—	—	+	Alk	A	A	—	A	A	A	—	—	—	—	—
	5	A	A	—	—	—	+	A & A C	A	—	A	A	A	A	—	—	—	—	—
	6	A	A	—	—	—	+	Alk	A	A	A	A	A	A	—	—	—	A	—
	7	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	9	A	A	—	—	—	+	A	A	—	A	A	A	A	—	—	—	—	—
78	1	A	A	—	—	—	+	Alk	A	A	A	A	A	—	—	—	—	—	—
	4	A	A	—	—	—	+	Alk	—	—	A	A	A	A	—	—	—	—	—
	6	A	A	—	—	—	+	Alk	A	—	—	A	A	A	A	—	—	—	—
	7	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
79	1	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	2	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	3	A	A	—	—	—	+	Alk	A	—	—	A	A	A	—	—	—	—	—
	4	A	A	—	—	—	+	Alk	—	—	A	A	A	A	—	—	—	—	—
	5	A	A	—	—	—	+	Alk	A	—	A	A	A	A	—	—	—	—	—
	6	A	A	—	—	—	+	Alk	A	—	A	A	A	A	—	—	—	A	—
	7	A	A	—	—	—	+	Alk	A	—	A	A	A	A	—	—	—	—	—
	8	A	A	—	—	—	+	Alk A C	A	—	A	A	A	A	—	—	—	—	—
	9	A	A	—	—	—	+	Alk	A	—	A	A	A	A	—	—	—	—	—

No. of Case	No. of Strain	Primary Series: Glucose	Mannite	Duleite	Saccharose	Salicin	Indol	Milk—14 days	Secondary Series: Sorbite	Rhamnose	Maltose	Levulose	Galactose	Mannose	Raffinose	Dextrin	Inulin	Adonite	Glycerin
82	2	A	A	—	—	—	—	A	—	A	A	A	A	A	A	—	—	A	—
	3	A	A	—	—	—	—	A	—	A	A	A	A	A	A	—	—	A	—
	4	A	A	—	—	—	—	A	—	A	A	A	A	A	A	—	—	A	—
	6	A	A	—	—	—	—	A	—	A	A	A	A	A	A	—	—	A	—
	7	A	A	—	—	—	—	A	—	A	A	A	A	A	A	—	—	A	—
	8	A	A	—	—	—	—	A	—	A	A	A	A	A	A	—	—	A	—
	9	A	A	—	—	—	—	A	—	A	A	A	A	A	A	—	—	A	—
	10	A	A	—	—	—	—	A	—	A	A	A	A	A	A	—	—	A	—
86	1	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
	2	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
	3	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
	4	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
	5	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
	6	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
	7	A	A	—	—	—	+	Alk	—	—	—	A	A	A	—	—	—	—	—
91	1	A	A	—	—	—	+	A	—	—	—	A	A	—	—	—	—	—	—
	2	A	A	—	—	—	—	A	—	—	A	A	A	—	—	—	—	—	—
	3	A	A	—	—	—	—	A	—	—	A	A	A	—	—	—	—	—	—
	4	A	A	—	—	—	+	A	—	—	—	A	A	—	—	—	—	—	—
	5	A	A	—	—	—	—	A	—	—	—	A	A	—	—	—	—	—	—
	6	A	A	—	—	—	—	A	—	—	—	A	A	—	—	—	—	—	—
	7	A	A	—	—	—	—	A	—	—	A	A	A	—	—	—	—	—	—
	8	A	A	—	A	—	—	A	—	—	—	A	A	—	—	A	—	—	—
	9	A	A	—	—	—	—	A	—	—	—	A	A	—	—	—	—	—	—
	10	A	A	—	—	—	—	A	—	—	A	A	A	—	—	A	—	—	—

APPENDIX II

In Appendix II is given, in a series of tables, the details of all the agglutination tests that were made with 99 strains of the Flexner-Y group all derived from different cases. In these tests only two immune sera were employed, one of which was prepared through the medium of Case 10, Strain 1, and the other of Case 86, Strain 1.

The exact titre of these sera against emulsions of the homologous bacillus appears to have varied at different periods. The following table gives some of the figures found, indicating the titres at various dates.

Serum prepared from Case 10, Strain 1		Serum prepared from Case 86, Strain 1	
Date	Titre	Date	Titre
9.6.14	3200 +	9.6.14	1600 + 3200 P
10.7.14	6400 +	9.7.14	6400 +
18.8.15	1600 + 3200 P	18.8.15	3200 + 6400 P
*14.6.17	4000 +	22.9.15	800 + 1600 P
30.6.17	1000 + 2000—	2.10.15	1600 + 3200 P
25.7.17	1000 + 2000—	9.10.15	800 + 1600 P
		*14.6.17	2000 + 4000 P
		30.6.17	1000 + 2000—

* This was most probably a freshly prepared serum.

In this table and throughout the appendix

\+ indicates complete agglutination.

P indicates partial agglutination.

— indicates that no agglutination took place.

T. S. indicates type strain.

The dates given of the experiments are approximate only; thus if a large series of agglutination tests were made, several days being occupied in carrying them out, the whole series of the tests are classed under the date of the first day.

To these tables is added a column in which the strain of bacillus with which the strain, under test, was found to be in agreement by the absorption test is also given.

TABLE 1

BACILLUS USED IN PREPARATION OF THE SERUM. CASE 10, STRAIN 1

Date of Experiment	9.6.14		10.7.14					2.10.15		20.10.15		9.10.15					20.6.17		Strain
Dilution of Serum	1 in 400	1 in 800	1 in 400	1 in 800	1 in 1600	1 in 3200	1 in 6400	1 in 400	1 in 800	1 in 400	1 in 800	1 in 50	1 in 100	1 in 200	1 in 400	1 in 800	1 in 500	1 in 1000	Case and strain with which agreement is shown by absorption test
No. of Case and Strain tested																			
Case 10 Strain 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	T. S.
1 5	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	..	...	10 1
6 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
7 1	+	+	...	...	...	...	...	+	+	+	+	...	...	...	...	...	...	...	10 1
8 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
9 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
11 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
17 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
19 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
22 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
23 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	..	...	...	10 1
24 1	+	+	+	+	+	+	+	—	—	+	+	...	...	...	...	...	...	...	10 1
26 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
28 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	..	...	10 1
38 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
39 1	...	...	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
40 1	+	+	+	+	P	—	—	—	—	—	—	+	+	+	+	+	—	—	170 1
47 1	—	—	...	...	...	...	...	—	—	+	+	+	+	+	+	+	...	...	— —
48 1	...	...	...	...	...	...	...	—	—	—	—	+	+	+	P	—	...	...	86 1
49 1	+	+	+	+	+	+	+	...	...	...	...	...	...	...	...	...	...	...	10 1
50 1	+	+	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	10 1
51 1	+	+	+	+	+	+	+	+	+	+	+	...	...	...	...	...	...	...	10 1
55 1	...	...	...	...	...	...	...	—	—	—	—	+	+	P	—	—	.	...	86 1
56 1	+	—	...	...	...	...	...	+	+	+	+	+	+	+	+	+	...	...	10 1
64 1	...	...	...	...	..	...	...	—	—	+	+	+	+	+	—	—	...	...	86 1
65 1	...	...	...	...		...	...	—	—	+	+	...	...	...	...	...	...	...	86 1
67 1	...	...	...	...	...	...	...	—	—	...	...	...	...	...	...	...	..	...	10 1
68 1	..	...	...	...	...	...	...	—	—	...	...	...	...	...	...	...	...	...	86 1
69 1	...	...	...	...	..	...	...	—	—	...	...	...	...	.	...	..	...	...	86 1

When the sign — is placed in this column it indicates that the strain tested did not agree with any of the strains from which the test sera had been prepared; the term 'test strain' indicates that a serum was prepared by means of the bacillus in question.

TABLE 1

BACILLUS USED IN PREPARATION OF THE SERUM. CASE 86, STRAIN 1

Date of Experiment	10.6.14		10.7.14					28.10.14		6.9.15		9.10.15					20.6.17	
Dilution of Serum	1 in 400	1 in 800	1 in 400	1 in 800	1 in 1600	1 in 3200	1 in 6400	1 in 400	1 in 800	1 in 400	1 in 800	1 in 50	1 in 100	1 in 200	1 in 400	1 in 800	1 in 500	1 in 1000
No. of Case and Strain tested																		
Case 10 Strain 1	—	—	...	...	...	...	...	+	+	—	—							
1 5	—	—	...	...	...	...	...	+	+	—	—							
6 1	—	—	...	...	...	...	...	+	—	—	—							
7 1	—	—	...	...	...	...	...	+	+	—	—							
8 1	—	—	...	...	...	...	...	+	+	—	—							
9 1	—	—	...	...	...	...	...	+	+	P	P							
11 1	—	—	...	...	...	...	...	+	+	P	P							
17 1	—	—	...	...	...	...	...	+	+	—	—							
19 1	—	—	...	...	...	...	...	+	+	P	P							
22 1	—	—	...	...	...	...	...	+	+	—	—							
23 1	—	—	...	...	...	...	...	+	+	—	—							
24 1	—	—	...	...	...	...	...	+	+	—	—							
26 1	—	—	...	...	...	...	...	+	+	—	—							
28 1	—	—	...	...	...	...	...	+	+	—	—							
38 1	—	—	...	...	...	..	...	+	+	P	P							
39 1	—	—	...	..	..	...	...	+	+	—	—							
40 1	—	—	...	...	...	...	...	—	—	—	—	...	...	...	...	...	—	—
47 1	—	—	...	...	...	...	...	+	+	P	P	+	+	P	—	—		
48 1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
49 1	—	—	...	...	...	...	...	+	+	P	P							
50 1	—	—	...	...	...	...	...	+	+	—	—							
51 1	—	—	...	...	...	...	...	+	+	P	P							
55 1	+	+	+	+	+	+	+	+	+	+	+							
56 1	—	—	...	...	...	...	...	+	+	—	—	+	P	—	—	—		
64 1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
65 1	+	+	+	+	+	+	+	+	+	+	+							
67 1	+	+	+	+	+	+	+	+	+									
68 1	+	+	+	+	+	+	+	+	+	+	+							
69 1	+	+	+	+	+	+	+	+	+	+	+							

TABLE 2

BACILLUS USED IN PREPARING THE SERUM. CASE 10, STRAIN 1

Date of Experiment	16.6.14		10.7.14					2.10.14		28.10.15		20.6.17		24.6.17		Case and Strain with which agreement is shown by absorption test
Dilution of Serum	1 in 400	1 in 800	1 in 400	1 in 800	1 in 1600	1 in 3200	1 in 6400	1 in 400	1 in 800	1 in 400	1 in 800	1 in 500	1 in 1000	1 in 500	1 in 1000	
No. of Case and Strain tested																
Case 70 Strain 1	...	...	...	...	...	...	...	—	—	...	...	—	—	...	...	86 1
74 6	...	...	...	...	...	...	...	—	—	...	...	...	...	...	...	86 1
75 9	...	...	...	...	...	...	...	—	—	...	...	...	...	...	...	86 1
76 1	...	...	...	...	...	...	...	—	—	...	...	...	...	...	...	86 1
78 7	...	...	...	...	...	...	..	—	—	...	...	...	...	...	...	86 1
79 2	...	...	...	...	...	...	...	—	—	...	...	—	—	...	...	86 1
79a 4	...	...	...	...	...	...	...	...	...	...	...	—	—	...	...	170 1
86 1	...	...	...	...	...	...	...	—	—	...	...	...	...	...	...	T. S.
91 1	+	+	+	+	+	+	+	...	...	+	+	...	...	...	...	10 1
92 10	+	+	+	+	+	+	+	...	...	+	+	...	...	...	...	10 1
100 1	+	+	+	+	+	+	+	...	...	+	+	...	...	...	...	10 1
102 1	+	+	+	+	+	+	+	...	...	...	...	...	...	...	...	not done
103 1	—	—	...	...	...	...	...	...	...	...	...	...	...	...	...	not done
104 1	+	+	+	+	+	+	+	...	...	...	...	...	...	...	...	not done
113 1	...	...	...	...	...	...	...	...	...	+	+	+	+	...	...	10 1
126 1	...	...	...	...	...	...	...	...	...	...	...	—	—	...	...	86 1
128 1	...	...	...	...	...	...	...	...	...	...	...	—	—	...	...	86 1
130 1	...	...	...	...	...	...	...	...	...	...	...	+	+	...	...	10 1
131 1	...	...	...	...	...	...	...	...	...	+	+	+	+	...	...	10 1
136 1	...	...	...	...	...	...	...	...	...	+	+	+	+	+	+	10 1
137 1	...	...	...	...	...	...	...	—	—	...	...	—	—	—	—	86 1
139 1	...	...	...	...	...	...	...	—	—	...	...	+	+	+	+	10 1
141 1	...	...	...	...	...	...	...	—	—	...	...	—	—	—	—	86 1
144 1	...	...	...	...	...	...	...	—	—	...	...	—	—	—	—	86 1
148 1	...	...	...	...	...	...	...	—	—	...	...	...	...	—	—	86 1
149 1	...	..	...	...	...	...	...	...	...	...	...	—	—	—	—	86 1
154 1	...	...	...	...	...	...	...	...	...	+	+	+	+	+	+	10 1
156 1	...	...	...	...	...	...	...	—	—	...	...	—	—	—	—	170 1
157 1	...	...	...	...	...	...	...	—	—	...	...	—	—	—	—	170 1

TABLE 2

BACILLUS USED IN PREPARING THE SERUM. CASE 86, STRAIN 1

Date of Experiment		10.6.14		9.7.14					28.10.14		6.9.15		20.6.17		24.6.17	
Dilution of Serum		1 in 400	1 in 800	1 in 400	1 in 800	1 in 1600	1 in 3200	1 in 6400	1 in 400	1 in 800	1 in 400	1 in 800	1 in 500	1 in 1000	1 in 500	1 in 1000
No. of Case and Strain tested																
Case 70	Strain 1	+	+	+	+	+	+	+	+	+	+	+	+	+		
74	6	+	+	+	+	+	+	+	+	+	+	+				
75	9	+	+	+	+	+	+	+	+	+	+	+				
76	1	+	+	+	+	+	+	+	+	+	+	+				
78	7	+	+	+	+	+	+	+	+	+						
79	2	+	+	+	+	+	+	+	+	+	+	+	+	+		
79a	4	...	...	...	...	...	...	...	...	...	—	—	—	—		
86	1	+	+	+	+	+	+	+	+	+	+	+				
91	1	—	—	...	...	...	...	...	+	+						
92	10	—	—	...	...	...	...	...	+	+	—	—				
100	1	—	—	...	...	...	...	...	+	+	—	—				
102	1	...	...													
103	1	...	...													
104	1	...	...													
113	1	...	...	...	...	...	...	...	...	...	—	—	—	—		
126	1	...	...	...	...	...	...	...	...	...	+	+	+	+		
128	1	...	...	...	...	...	...	...	...	...	+	+	+	+		
130	1	...	...	...	...	...	...	...	...	...	?	?	—	—		
131	1	...	...	...	...	...	...	...	...	...	—	—	—	—		
136	1	...	...	...	...	...	...	...	...	...	P	P	+	+	+	+
137	1	...	...	...	...	...	...	...	...	...	—	—	—	—	+	+
139	1	...	...	...	...	...	...	...	...	...	?	?	—	—	—	—
141	1	...	...	...	...	...	...	...	...	...	+	+	+	+	+	+
144	1	...	...	...	...	...	...	...	...	...	+	+	+	+	+	+
148	1	...	...	...	...	...	...	..	...	...	—	—	...	...	+	+
149	1	...	...	...	...	...	...	...	...	...	...	...	+	+	+	+
154	1	...	...	...	...	...	...	...	...	...	—	—	—	—	+	+
156	1	...	...	...	...	...	...	...	...	...	P	P	—	—	—	—
157	1	...	...	...	...	...	...	...	...	...	P	P	—	—	—	—

TABLE 3

BACILLUS USED IN PREPARING THE SERUM. CASE 10, STRAIN 1

Date of Experiment	2.10.15		25.6.17		11.9.17		Case and Strain with which agreement is shown by absorption test	
Dilution of Serum	1 in 400	1 in 800	1 in 500	1 in 1000	1 in 500	1 in 1000		
No. of Case and Strain tested								
Case 159 Strain 1	P	P	—	—	..	...	170	1
161	P	P	—	—	—	—	170	1
164	P	P	+	+	...	...	170	1
165	P	P	—	—	—	—	170	1
167	+	+	—	—	...	...	170	1
168	+	+	+	+	...	...	10	1
169	+	+	+	+	...	...	10	1
170	—	—	—	—	—	—	T. S.	
172	—	—	—	—	...	...	311	1
176	...	...	—	—	—	—	86	1
178	...	...	—	—	—	—	86	1
184	—	—	—	—	—	—	170	1
185	...	...	—	—	—	—	86	1
189	...	...	—	—	—	—	86	1
196	...	..	—	—	—	—	86	1
198	P	—	—	—	—	—	—	—
200	—	—	—	—	—	—	311	1
219	—	—	—	—	—	—	311	1
221	...	...	—	—	—	—	86	1
222	...	...	—	—	—	—	86	1
225	—	—	—	—	—	—	311	1
231	—	—	—	—	—	—	311	1
252	—	—	—	—	—	—	275	2
260	—	—	—	—	—	—	311	1
265	—	—	—	—	—	—	—	—
268	—	—	—	—	—	—	311	1
269	+	+	+	+	+	+	10	1
270	+	—	—	—	—	—	311	1
271	—	—	—	—	—	—	86	1

TABLE 4

BACILLUS USED IN PREPARING THE SERUM. CASE 10, STRAIN 1

Date of Experiment	16.6.17		11.9.17		Case and Strain with which agreement is shown by absorption test	
Dilution of Serum	1 in 500	1 in 1000	1 in 500	1 in 1000		
No. of Case and Strain tested					C.	S.
Case 275 Strain	—	—	—	—	T. S.	
290	...	...	—	—	311	1
291	...	...	—	—	86	1
307	+	+	+	+	10	1
311	—	—	—	—	T. S.	
318	+	+	+	+	10	1
319	+	+	+	+	10	1
321	+	+	+	+	10	1
322	+	+	+	+	10	1
325	+	—	+	+	10	1
326	±	±	—	—	86	1
336	+	+	+	+	10	1

TABLE 3

BACILLUS USED IN PREPARING THE SERUM. CASE 86, STRAIN 1

Date of Experiment	6.9.15		25.6.17		11.9.17	
Dilution of Serum	1 in 400	1 in 800	1 in 500	1 in 1000	1 in 500	1 in 1000
No. of Case and Strain tested						
Case 159 Strain 1	P	P	—	—		
161	+	—	—	—	—	—
164	—	—	—	—		
165	P	P	—	—	—	—
167	—	—	—	—		
168	+	—	+	+		
169	—	—	—	—		
170	—	—	—	—	—	—
172	—	—	—	—		
176	+	+	+	+	+	+
178	...	...	+	+	+	+
184	P	P	—	—	—	—
185	+	+	+	+	+	+
189	...	...	+	+	+	+
196	+	+	+	+	+	+
198	—	—	—	—	—	—
200	—	—	—	—	—	—
219	—	—	—	—	—	—
221	+	+	+	+	+	+
222	+	+	+	+	+	+
225	—	—	—	—	—	—
231	—	—	—	—	—	—
252		...	—	—	—	—
260	P	P	—	—	—	—
265	P	P	—	—	—	—
268	—	—	—	—	—	—
269	P	P	—	—	—	—
270	+	+	—		—	—
271	P	P	+	+	+	+

TABLE 4

BACILLUS USED IN PREPARING THE SERUM. CASE 86, STRAIN 1

Date of Experiment	16.6.17		11.9.17	
Dilution of Serum	1 in 500	1 in 1000	1 in 500	1 in 1000
No. of Case and Strain tested				
Case 275 Strain	—	—	—	—
290	+	+	—	—
291	+	+	+	+
307	—	—	—	—
311	—	—	—	—
318	—	—	—	—
319	—	—	—	—
321	—	—	—	—
322	—	—	—	—
325	—	—	—	—
326	—	—	+	+
336	—	—	—	—

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MEDICAL RESEARCH COMMITTEE

Alcohol: its absorption into and disappearance from the blood under different conditions

Approved for publication by the Medical Research Committee, February 7, 1919.

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INTRODUCTION

THE work described in the present Report was undertaken at the request of the Central Control Board (Liquor Traffic) by Dr. Edward Mellanby, whose services were lent, with the provision of the necessary expenses, by the Medical Research Committee. The Committee are glad to publish these results in their present form at the suggestion of the Board.

The auspices under which this investigation was begun and carried out made it natural that the experiments should be planned with special reference to practical issues. Their primary aim was to decide how far the circumstances in which a given amount of alcohol is consumed can affect the degree of intoxication produced by it. The investigation, so far as it is described in the present Report, was confined to the use of dogs as subjects, and Dr. Mellanby is careful to emphasize the difficulty of estimating or expressing the intensity of intoxication as shown by an animal in any terms which could be applied with certainty to a human being. His statements are based upon objective facts, and in the main upon the study of a variable which can be accurately estimated and quantitatively expressed. He has determined, in various circumstances, the concentration of alcohol in the blood found at known periods after giving a definite dose by the mouth. That the various factors shown to affect the results in a dog are likely to have a corresponding influence in man is a proposition that may well be granted. We learn indeed that preliminary experiments already carried out on human beings indicate that the results are strictly comparable. That measurements of the concentration of alcohol in the blood, and of the velocity with which a maximal concentration is reached, should yield information as to the degree of intoxication associated with the consumption of a beverage under this or that condition, is a reasonable assumption.

Dr. Mellanby shows that the maximal concentration in the blood, which occurs very soon after the alcohol is consumed, is, within certain limits, proportional to the amount taken. On the other hand, and because the disappearance of the alcohol from the blood is remarkably slow—an interesting and important fact illustrated in all the observations described—a given amount of spirit produces the same maximal concentration whether it be taken in one dose or in divided doses at intervals which may extend to two hours. The effect is cumulative. A definite amount of alcohol taken in a dilute form accumulates in the blood more slowly and reaches a lower maximum than when it is taken undiluted. The weaker the beverage therefore the more actual

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alcohol must be consumed in order that a definite degree of intoxication should be reached.

While this effect of dilution is well established by the experiments, it is noteworthy that the consumption of water or other fluids a few hours before a dose of alcohol is taken leads to more rapid absorption of the latter, and consequently—for a given dose—to more intense intoxication.

Food-stuffs inhibit intoxication in consequence of their action in delaying absorption from the alimentary canal. The most effective food-stuff in this respect is milk. Its specific influence in delaying absorption more than counterbalances its general effect as a fluid, and Dr. Mellanby comments upon the striking differences observed in the effects of a dose of alcohol when given two hours after the consumption of half a litre of water and after half a litre of milk respectively. In the first case a dog may become incapable of standing or walking, in the latter case it may show no sign whatever of unsteadiness.

Such points as these are mentioned here in illustration of the practical bearing of Dr. Mellanby's results. The student of metabolism will find much of interest in the facts, so well established by the experiments, that alcohol disappears from the circulation with remarkable slowness and at a rate which is independent of the concentration. Of no less interest is the evidence which suggests—though doubtless it fails to prove—that alcohol is incapable of yielding energy to the muscles.

Medical Research Committee,
15 Buckingham Street,
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June 2, 1919.

ALCOHOL: ITS ABSORPTION INTO AND DISAPPEARANCE FROM THE BLOOD UNDER DIFFERENT CONDITIONS.

By Edward Mellanby, M.A., M.D. (Cantab.) *(from the Household and Social Science Department, London University).*

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I. Introduction.

The experimental work described in the following pages is the result of a request by the Chairman of the Central Control Board (Liquor Traffic) to supply certain information in order that the policy of controlling the sale of liquor might be guided and assisted by the results of scientific inquiry. The request was of a comprehensive nature, and presented such problems as the effect of dilution on the intoxicating properties of alcohol, the modifying action (if any) of food-stuffs at different stages of digestion on

alcoholic intoxication, variations in the effects of beverages imbibed, and so on. It will be seen that definite answers have been supplied to some of these questions, at least so far as experimental animals (dogs) are concerned. As regards some points, the work has provided information along lines which were unexpected at the outset, and, in some cases, has presented a picture seen at a different angle from that of other workers on alcohol, with the result that new conceptions of the physiological action of this substance seem justifiable.

It is necessary to point out the limitations of work of this type. In all cases alcohol has been placed directly into the stomach of dogs and the amount in the blood estimated at different times. The results therefore only give an accurate account of the rate of absorption of alcohol from the alimentary canal and its rate of disappearance from the blood-stream. Now, although there is an unquestionable relationship between alcohol in the blood and intoxication, it is not certain that the relation between the two is close enough to allow the latter to be strictly determined from the former. This fact would not be of much importance if there were as accurate a measure of intoxication as there is of alcohol in the blood, but this is not the case. It is evident that even in the case of a man it is difficult to get a complete measure of a nervous defect like intoxication. In dogs it has been impossible under the present conditions of the work. This point will be considered in more detail later, but meantime it is clear that, although from the point of view of the Central Control Board, the answer to the questions presented should be given in terms of intoxication rather than of alcohol in the blood, it is just at this point the work fails. A further criticism, although this I consider of less importance, is that the results obtained from dogs may not apply to man.[1]

These limitations suggest that this work is to be regarded as a basis for other work rather than as offering definite solutions to the problems presented. Great differences have been observed in the amounts of alcohol in the blood under varying conditions, and, incidentally, great differences in intoxication, but it seems to me that the experiments should be extended to men, using these results as the basis. In future experiments the psychologist should apply his methods for measuring symptoms of intoxication, while, at the same time, estimations of the alcohol in the blood should be made so as to control and confirm the present work.

Finally, it may be added that the present investigation has been led a short way along many side paths, which, if followed up, promise interesting information. It is possible that further work will be undertaken to open up these new lines.

II. Experimental Procedure.

The experiments to be described have been made on four dogs which will be known throughout as brown, large black, small black,

[1] I have more recently repeated some of the experiments on man and, except that he is more susceptible to alcohol, the results so far obtained are comparable.

and white. The weights of the dogs have been approximately as follows:

Brown . .	13·0 to 14·6 kilograms.
Large black . . .	12·5 „
Small black . . .	11·35 „
White	10·0 „

Under war conditions these weights have varied from time to time.

Definite quantities of alcohol made up to varying strengths according to the nature of the experiment were placed directly into the stomach by a tube passed down the oesophagus.

In order to do this the dog was placed in a sack held firmly at the neck. As a rule there was no difficulty in this operation. When large quantities of fluid were used—in some cases 1,200 c.c. of fluid were poured into the stomach—it was essential to proceed slowly and allow the stomach to adapt itself to the large volume. Otherwise the dog would vomit large quantities. The time taken for the injection varied from 1 to 5 minutes according to the volume of fluid used. After injecting the alcohol it is essential that the dogs should be closely watched, more particularly if a strong alcoholic solution, i.e. 20 per cent. or over, be used. The irritating action of the alcohol on the mucous membrane of the stomach often causes the dog to vomit small quantities, and this deprives the experiments of any value; for, even if only 1 c.c. of alcohol is lost in this way, it makes a considerable difference to the alcohol-in-the-blood results. With dilute alcoholic solutions this danger is not so great, but in all cases it is advisable to keep the dogs quiet for about 10 minutes after the injection, and to watch them closely during the next hour. Unless the animals are very intoxicated the danger of vomiting is small after this time, but, if marked intoxication is produced, the danger of vomiting is never absent during the experiment.

In experiments of this type it is clear that so many variable factors present themselves that precautions must be taken to keep the animals in as uniform a condition as possible. The achievement of this object has been only partially successful, so that, although there may be many other points of interest in the results obtained, only those points are mentioned in which there is fair unanimity among the different dogs. It was necessary to have the stomach and small intestine in a definite condition according to the experiment, so that, except where otherwise stated, the dogs were each given 1 lb. of meat at 2 p.m. on the day prior to the experiment. When this was eaten (always a matter of minutes) the water in the kennels was also withdrawn, and no other food or water given until the experiment started, usually at 10 a.m. the following day. At the time of the experiment, therefore, the stomach and small intestines were empty except for that food, the influence of which on alcohol absorption was being tested.

The varying temperature according to the time of year must have had some effect on the development of thirst in the dogs. Except that they were not allowed to exercise after the withdrawal of water, this question of thirst, which will be seen to be of some importance as regards the rate of absorption of alcohol, has not been as well controlled as is desirable. A greater source of error, viz. the actual drinking of water for a period of hours before the experiment has, however, been prevented. In order to control this question of thirst in a satisfactory way, it is necessary to give a constant diet, limit the activities of the animal, and if possible keep it at a constant temperature. It was not possible to keep the animals at a constant temperature throughout the year, but this difficulty was overcome by the carrying out of numerous control experiments.

After the injection of the alcohol into the stomach, samples of blood of 5 to 7 c.c. were withdrawn at different intervals.[1] These intervals were short in the early stages, that is when the rate of absorption into the blood-

[1] Gréhant (*Compt. rend. Soc. de Biol.*, Par., 1899, **51**, 946, and 1900, **52**, 894) has used this method of making a series of analyses of alcohol in the blood at intervals.

stream was rapid, but were longer as the experiment proceeded. Samples were taken usually at half-hourly intervals during the first $1\frac{1}{2}$ hours, then at 1 hour, $1\frac{1}{2}$ hours, and 2 hours intervals.

The most satisfactory method of withdrawing blood is to make a small cut of about $\frac{1}{8}$ in. depth at the edge of the ear and allow the blood to drop into a weighing bottle. When the requisite quantity is obtained, the cut is held with cotton wool until coagulation is produced. Further samples can be easily obtained from the same cut after rubbing off the clot.

This method is easy and has many advantages over the withdrawal of blood by venepuncture in the case of dogs. The weighing bottles into which the blood was dropped each contained 1 c.c. of 7 per cent. sodium citrate solution. This effectively prevented blood coagulation. The estimation of the alcohol in the samples of blood was started as soon as possible after withdrawal. This usually took place on the day following the animal experiment. Overnight the blood was kept in a cold place. In hot weather it was necessary to keep the blood in an ice-chest until distilled.

Estimation of Alcohol in the Blood.

For the estimation of alcohol in the blood the method adopted by Pringsheim [1] was used. The blood was distilled under reduced pressure, the distillate was then heated up in a stoppered bottle with a standard solution of $K_2Cr_2O_7$ and, after cooling, the excess of potassium bichromate not reduced by the alcohol was estimated by titrating with an acid solution of ferrous ammonium sulphate.

This method has slowly evolved as the result of many researches on alcohol by different investigators. Bodländer [2] appears to have first used $K_2Cr_2O_7$ and H_2SO_4 for oxidizing the alcohol. Cotte [3] was the first to titrate with ferrous ammonium sulphate, using $K_3FeC_6N_6$ as an indicator. An historical account of the development of the method is given by Pringsheim.

Strengths of solutions and the general technique employed followed closely the recommendations of Pringsheim. The potassium bichromate solution contained 14·725 grammes in 2 litres. Pringsheim [1] states that 22·6 c.c. of this solution is reduced by 50 cm. of alcohol, and this figure has been used in the calculations.

The ferrous ammonium sulphate solution contained 39·24 grammes of this substance in 2 litres, and to this was then added 100 c.c. of concentrated sulphuric acid. Standarized against the $K_2Cr_2O_7$ solution it was found that 20 c.c. of the latter was equivalent to about 63 c.c. of the ferrous ammonium sulphate solution. Although the presence of the sulphuric acid conferred stability on the ferrous ammonium sulphate solution, the two solutions were compared in every experiment lest any alteration in strength had taken place.

The blood was washed from the weighing bottles into a litre flask which was connected up to a double surface condenser. The distillate was received into a large boiling-tube surrounded by an ice-salt mixture. Between this tube and the water-pump another tube was placed containing about 10 c.c. of water also surrounded by ice. Air was evacuated by the pump and the blood allowed to distil at a temperature of 50°–55° C. The greatest trouble met with in this work was the constant frothing up of the blood. The trouble was never overcome, and in every distillation the blood had to be carefully watched. A stream of air was allowed to play on the froth when it got too high in the flask. No trace of blood other than its volatile contents must be allowed to pass from the flask into the distillate. If some of the froth bubbles over, the whole lot must be re-distilled until a clear colourless distillate is obtained. The blood was distilled almost to dryness, and the condenser then well washed with distilled water and the washings added to the distillate. To this also was added the water from the second test-tube through which the air had been drawn. The washings and distillate were placed in

[1] Pringsheim, *Biochem. Ztschr.*, Berl., 1908, **12**, 141.
[2] Bodländer, *Arch. f. d. ges. Physiol.*, 1883, **32**.
[3] Cotte, Abstract in *Chem. Ztschr.*, **21**, 254, referred to by Pringsheim.

a reagent bottle, 20 c.c. of the standard $K_2Cr_2O_7$ was then added, together with 4 c.c. of concentrated sulphuric acid. After shaking, a cork was tied in the bottle, and this was then heated in a water bath at 100° C. for $1\frac{1}{4}$ hours. After cooling, the solution was titrated with ferrous ammonium sulphate. The end-point for this titration requires experience before absolutely reliable results are obtained. Ferrous ammonium sulphate is added to the bichromate mixture until the green colour just turns blue. The end-point is reached if a drop of freshly-prepared solution of potassium ferricyanide meeting a drop of the mixture being tested, on a filter paper, causes a faint prussian blue to develop. The ferrous ammonium sulphate solution is added drop by drop at this stage until the prussian blue reaction on the filter paper is obtained. It is difficult at first to appreciate the slight differences between the various shades intermediate between real green and undoubted blue, but experience overcomes this difficulty. Considering the small amounts of alcohol in the blood, the method gives fairly accurate results.

The researches of previous workers on this subject have made it clear that the blood always contains a small quantity of a volatile reducing substance which may be alcohol. For instance Schweisheimer[1] states that these reducing agents are equivalent to quantities of alcohol varying from 0·02955 per mille to 0·03686 per mille. Rosemann[2] suggests that, if alcohol, it is probably due to bacterial decomposition in the intestine. In any case the amount is too small to have any interfering action on the experimental results to be recorded.

III. Relation between Alcohol in Blood and the Amount drunk.

Fig. I illustrates the varying concentration to which alcohol in the blood attains according to the quantity taken. The following tables representing the results recorded in Fig. I, together with similar experiments on other dogs, will probably indicate more clearly the relation between the alcoholic concentration in the blood at its maximum and the amount drunk.

Amount of alcohol taken.	Maximum concentration in blood cm. per 100 grammes blood.	Time after taking alcohol.	Alcohol in blood at maximum point per 10 c.c. of alcohol drunk.
Large brown. *Weight* 13 *kilograms.*			
55 c.c.	464 cm.	2 hours	84 cm.
50	445	1	89
30	265	$1\frac{1}{2}$	88
20	153	$1\frac{1}{4}$	77
Large black. *Weight* 12 *kilograms.*			
50 c.c.	447 cm.	2 hours	89 cm.
30	277	$2\frac{1}{4}$	92
Small black. *Weight* 10 *kilograms.*			
40 c.c.	530 cm.	$1\frac{1}{2}$ hours	132 cm.
30	398	$1\frac{3}{4}$	133
20	243	$1\frac{1}{2}$	121
Small white. *Weight* $10\frac{1}{2}$ *kilograms.*			
40 c.c.	504 cm.	1 hour	126 cm.
30	387	1 hour	129

[1] Schweisheimer, *Deutsches Arch. f. klin. Med.*, Leipz., 1913, 109.
[2] Rosemann, *Oppenheimers Handbuch der Biochemie*, 1911, 4(1), 422.

As regards the maximum concentration it will be seen:

(1) That when the alcohol taken varies between 55 c.c. and 30 c.c., the amount in the blood at its maximum is proportional to the amount taken.

(2) That when the alcohol is taken in smaller amounts, i.e. 20 c.c., then this relationship no longer holds, and there is less in the blood than would be expected. It appears as if some demand was first made on the small quantity of alcohol by some other tissues before the blood received its portion. Part of this difference can also be explained by the proportionate greater loss by oxidation during the period before the maximum is attained in those experiments when smaller quantities of alcohol were given.

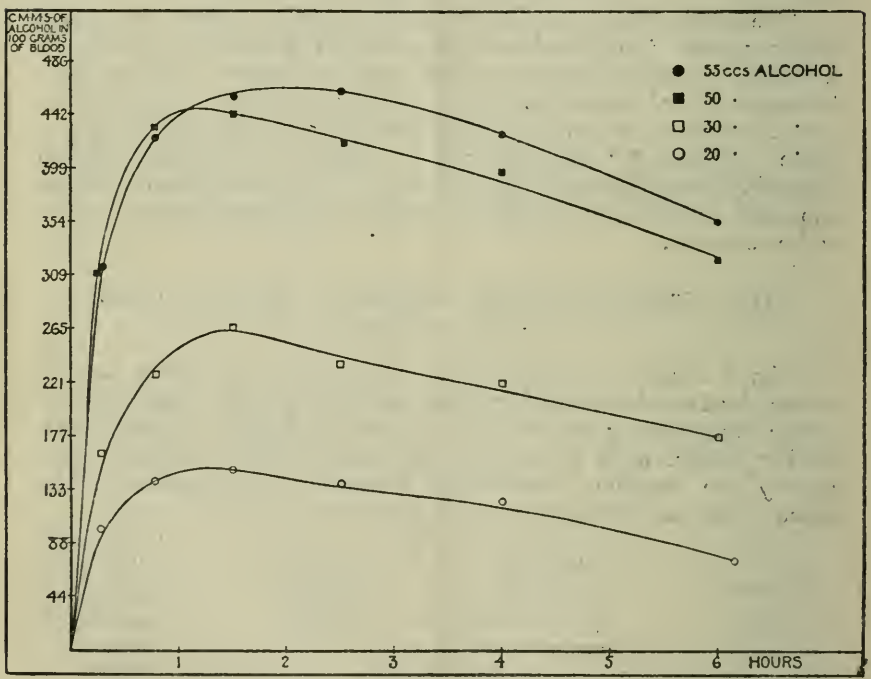

FIGURE I.

It will be further observed that the amount of alcohol in the blood of the different dogs after drinking equal quantities of alcohol is not proportional to their body weights. The smallest of these dogs received an average increased concentration of 128 cm. per 100 grammes of blood for each 10 c.c. of alcohol drunk, and the largest an increase of 84 cm. for the same amount. The weights of these dogs were respectively 10·5 kilograms and 13 kilograms, so that the amount of alcohol in the blood is not inversely proportional to the dogs' weight, but the amount in the blood of the smaller dog is relatively much higher than in the larger one. Assuming that the results obtained in these particular dogs are not a coincidence, and further, if the supposition is accepted that there is a relationship between alcohol in the blood and intoxication,

then the smaller animal would be expected to be more intoxicated with a less quantity of alcohol than its weight would demand. It was certainly the case with these dogs that the smaller animals became more intoxicated with proportionately less alcohol than the heavier dogs. Applying such results to men, other conditions such as tolerance, &c., being equal, it is probable that if a small and a big man drank quantities of alcohol proportional to their weights, the former would be intoxicated at a time when the latter would be sober.

It is interesting also to notice the alcoholic relationships in each particular dog when in a fat and a lean condition. At one period of the work the dogs lost weight and at a later period became much fatter. The following figures illustrate the alcohol distribution in the lean and fat conditions:

Small black.

May, 1918. Weight 10 kilograms. Increased amount of alcohol in blood at maximum per 10 c.c. taken = 133 cm. per 100 grammes blood.

August, 1918. Weight 11 kilograms. ,, = 118 ,,

Ratio of body weights of dog = $\frac{10}{11} = 0{\cdot}91$

Inverse ratio of alcohol concentrations = $\frac{118}{133} = 0{\cdot}90$

Large brown.

May, 1918. Weight 11·75 kilograms. Increased amount of alcohol in blood at maximum per 10 c.c. taken = $\frac{475}{5} = 92$ cm. per 100 grammes blood

August, 1918. Weight 13·5 kilograms. ,, = $\frac{420}{5} = 84$,,

Ratio of body weights of dog = $\frac{11{\cdot}75}{13{\cdot}5} = 0{\cdot}87$

Inverse ratio of alcohol concentrations = $\frac{84}{92} = 0{\cdot}91$

In the case of each dog the ratio of the alcohol concentration in the blood to the body weight is practically constant, whether it be in a fat or a lean condition, or, in other words, the amount of alcohol in the blood per unit of alcohol drunk in any single dog when its weight alters is inversely proportional to its weight.

The reaction to alcohol, therefore, in the case of an animal whose weight varies is not the same as when a comparison is made between a small or a larger animal. In the individual animal, the amount of alcohol in the blood varies inversely as its weight alters, whereas in comparing different animals, the smaller one accumulates a greater concentration of alcohol in its blood than its weight would warrant when quantities of alcohol proportional to body weight are taken by mouth.

It has been pointed out by Gréhant[1] that the amount of alcohol in the blood of an animal after a definite quantity has been drunk

[1] Gréhant, *Compt. rend. Soc. de Biol.*, Par., 1881, 1896, 1899.

is the amount that would be expected assuming that the alcohol is evenly distributed throughout the body. For instance when his dogs received 5 c.c. and 4 c.c. of alcohol per kilo body weight, the alcohol content of the blood was respectively 0·5 per cent. and 0·4 per cent. In my experiments the weight of the brown dog was 13·5 kilograms, and the amount of alcohol in 100 grammes of blood for each 50 c.c. of alcohol drunk was 420 cm. On the above assumption the blood ought to have contained 370 cm. With a smaller dog, viz. small black, the discrepancy is rather greater, the actual amount of alcohol in the blood at its maximum being 354 cm. per 100 grammes of blood and the theoretical quantity being 273 cm. It would appear, therefore, that Gréhant's results are of the nature of a coincidence, and that there is not a sufficient basis to warrant the general assumption as above expressed being applied to all dogs.

Summary.

(1) In any individual dog, the amount of alcohol in unit volume of blood at its maximum is proportional to the amount drunk if taken with stomach and small intestine empty. This only holds if the alcohol drunk is greater than 2 c.c. per kilogram weight. Below this there is less alcohol in the blood.

(2) Comparing a large and a small dog, if both receive an amount of alcohol proportional to their body weight, the blood of the smaller dog contains at its maximum a relatively larger amount of alcohol in unit volume.

(3) If a dog varies in weight, then, after receiving the same amount of alcohol on different occasions, the amount in unit volume of blood is inversely proportional to its body weight.

IV. The Rate of Disappearance of Alcohol from the Blood.

Fig. I shows, as in fact do all the curves, how slow is the rate of disappearance of alcohol from the blood compared to its rate of accumulation. This point is, however, most evident in Fig. II. where the experiment was continued for about 20 hours. It will be seen in Curve A that, after taking 50 c.c. of alcohol, this substance reaches a maximum in an hour, but that, even at the end of 19 hours, some remains in the blood, i.e. about 33 cm. per 100 grammes of blood. It might be thought that this small amount represented an error in estimation, and in order to determine this point a further injection of 50 c.c. of alcohol was again given 18½ hours after the first injection. Curve B is the result obtained after this second injection of alcohol. It will be seen that a higher concentration of alcohol in the blood is produced than on the previous day, the difference being no doubt due to the small amount remaining from the first injection. Here, then, we have an accumulative effect produced by a second alcoholic injection in consequence of the fact that the first 50 c.c. had not been fully oxidized by the animal in 18½ hours. It may be further mentioned that evidence of an accumulative effect was also

obtained in the more marked intoxication of the dog following the second day's injection. In the case of this dog, we have an animal, whose weight is 13·5 kilograms, taking 20 hours to get rid of 50 c.c. of alcohol from its blood, and presumably therefore from its body, that is, at the rate of $2\frac{1}{2}$ c.c. per hour or 0·185 c.c. per kilogram weight per hour. This slow rate of disappearance of alcohol from the blood has been observed by Gréhant and other workers on the subject. It is a point of some importance, for it can readily be understood how easy it must be to produce intense intoxication by a second drink of an alcoholic beverage which, had it been the first drink, would have had no such result, although

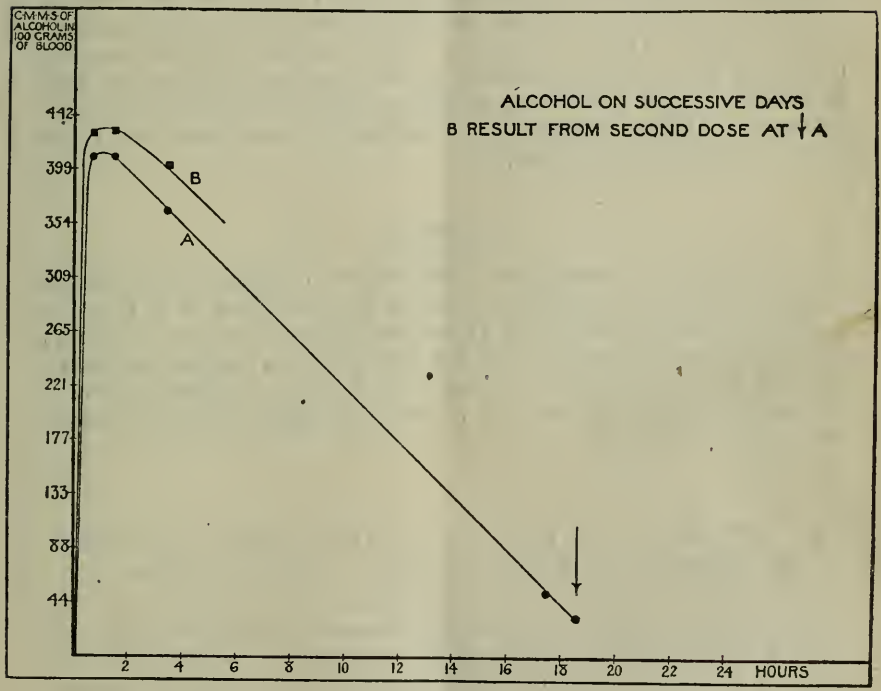

FIGURE II.

the interval between the drinks may have been many hours. This fact also forms, no doubt, part of the physiological basis of the feeling of ill-health on the morning following a carouse, and the gradual development of a feeling of well-being as the day progresses and the alcohol is cleared out of the body.

Calorimetric experiments, and more particularly those of Atwater and Benedict,[1] demonstrate that this disappearance of alcohol from the body involves its almost complete oxidation, so that we can speak of the oxidation of alcohol as being a slow process, and going on at the rate of 0·185 c.c. per kilogram weight per hour in this particular dog's body.

Fig. II shows another point worthy of comment. After reaching a maximum the Curve A descends in a straight line to the abscissa.

[1] ATWATER and BENEDICT, *Mem. Nat. Acad. Sc.*, Wash., 1902, **8**, 231.

This means that the rate of oxidation is constant throughout the whole period, and this is the case in spite of the fact that the amount of alcohol in the body is getting progressively less. The interpretation of this fact is therefore that, whatever the amount of alcohol in the body, the rate of oxidation is constant, or, in other words, the rate of oxidation of alcohol is independent of the amount drunk. Lest Curve A of Fig. II be regarded as a coincidence, reference to Fig. I will clearly corroborate this fact. In Fig. I we see curves representing the rates of oxidation of alcohol after 55, 50, 30, and 20 c.c. of alcohol respectively have been drunk by the same dog. There is a striking parallelism between the descent of the different curves which means that, in unit time, practically the same amount of alcohol is being oxidized in each case. Other evidence of the constancy of the alcohol oxidation and its independence of the amount in the body will be forthcoming in the course of this paper, and its further significance more fully discussed when alcohol is considered from the point of view of a food-stuff.

Summary.

The rate of accumulation of alcohol in the blood after entrance to the stomach is rapid, and reaches its maximum in $\frac{1}{2}$ hour to 2 hours. The rate at which it leaves the body is slow, and is at the approximate rate of 0·185 c.c. per kilogram weight per hour. Thus a dog of 13·5 kilograms takes 20 hours to get rid of 50 c.c. of alcohol. This dog was not at rest throughout, but could move about a room at will.

V. The Effects of drinking a given Amount of Alcohol at once and in Portions taken at Different Times.

A common belief among those interested in alcoholic intoxication is that symptoms produced by a definite quantity of alcohol may be avoided to some extent if it is gulped, but that, if the same amount is drunk slowly or sipped, then the worst may happen. It is impossible to reproduce exactly and test by experiment this condition in an animal, but several attempts were made to simulate the condition by comparing the results following the giving to an animal all the alcohol at once, and in four portions at intervals of about 10 minutes. In no case was any evidence obtained that taking the alcohol in portions at short intervals increased the amount and rate of accumulation of alcohol in the blood. Nor did the symptoms of intoxication appear to be increased. It is difficult, therefore, to believe that taking alcohol at one gulp can have an effect very different from that which results when it is sipped over a period of 40 minutes.

Further experiments were made in which the intervals between the drinks were gradually lengthened, and the results are given in Fig. III. Here the same total quantity of alcohol was given under the following conditions:

A. 250 c.c. of a 20 per cent. solution of alcohol (i. e. 50 c.c. absolute alcohol) at once.
B. The same quantity in two equal portions at an interval of 3 hours.
C. The same quantity in three equal portions at intervals of 1 hour.
D. The same quantity in three equal portions at intervals of 2 hours.

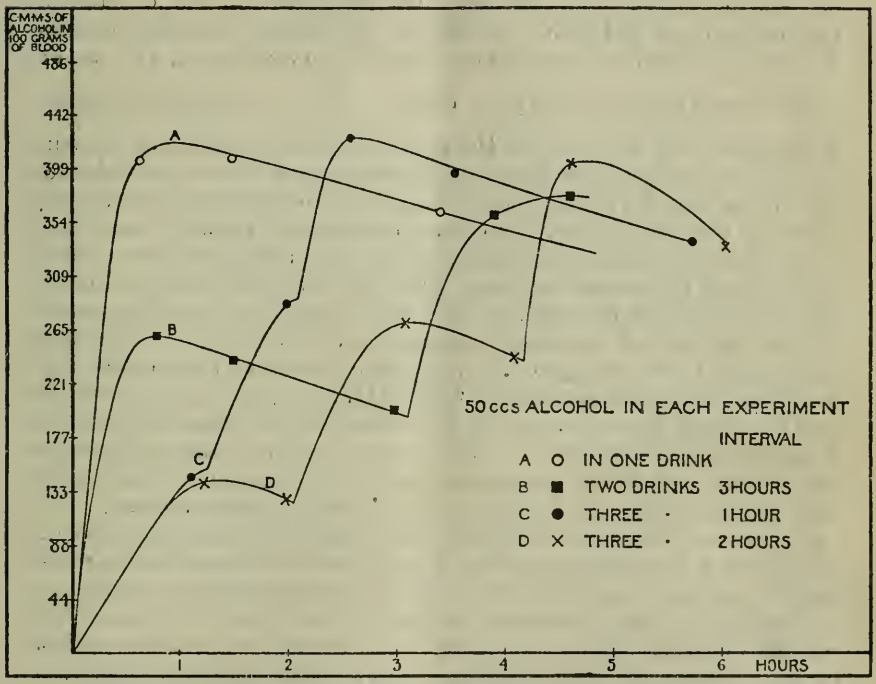

FIGURE III.

If we look at Curves A, C, and D we see the salient points to be:

(1) The same maximum concentration of alcohol is reached. Of course in each experiment the time of maximum concentration varies.
(2) The rate of accumulation of alcohol in the blood increases as the amount increases.
(3) The rate of accumulation when the alcohol in the blood approaches its maximum is approximately the same.
(4) At the end of each experiment, i. e. about 6 hours after the alcohol was first given, the amount remaining in the blood is practically the same.

If we now look at Curve B we see that these facts no longer hold, for (1) the maximum concentration in B is slightly lower than in A, C, D; (2) the rate of accumulation of alcohol in the

blood after the second drink (3 hours after the first) is much slower than after the second and third drinks of C and D.

These facts, which seem unexpected at first sight, involve several points of interest, and can only be understood when the effect of water on alimentary absorption is appreciated. This latter condition will be discussed later in the paper, but it may be well to consider the facts as expressed in Fig. III without offering any detailed explanation.

Alcohol, then, accumulates more rapidly as the amount in the blood increases when the interval between the drinks is not more than 3 hours. In Curve D (interval between drinks 2 hours), during the first 75 minutes of the experiment, 140 cm. of alcohol were added to 100 grm. blood, or $\frac{140}{75} = 1{\cdot}9$ cm. per minute. After the third injection of the same quantity of alcohol, 158 cm. were added to 100 grm. blood in 30 minutes, or 5·3 cm. per minute. It is clear also that this difference cannot be explained by assuming that, in the latter case, there was unabsorbed alcohol remaining over from the previous injections, for the shape of the earlier portions of the curve indicates that the first injection was completely or almost completely absorbed from the alimentary canal before the second injection was given, and the second injection before the third was given. It appears therefore that, under the conditions of the experiments C and D, the more alcohol there is in the blood the more easily is further alcohol absorbed into it from the alimentary canal. When, however, the interval between the drinks is 3 hours or longer, then there is no acceleration of absorption of the second drink, and in fact the rate is slowed.

The two results, (1) that the same maximum concentration of alcohol in the blood was reached, and (2) that at the end of each experiment there remained practically the same amount of alcohol in the dog's body, point to another fact, viz. that the rate at which alcohol disappears from the body is constant, and is independent of the amount of concentration. For instance, comparing Curves A and D, it is evident that for the first 2 hours in Curve A there is three times as much alcohol in the dog's body as in D, and in the next 2 hours one-third more, yet at the end of 6 hours the alcohol remaining is the same. If the tissues burned up the alcohol at a greater rate when more was present, then less alcohol would have been found in the blood at the end of A than C. This is not the case, and therefore the rate of combustion must be independent of the amount drunk.

The facts that, when the interval between the drinks is not longer than 3 hours the maximum concentration of the alcohol in the blood is ultimately the same, and that the rate of accumulation at and before the maximum point in each case is the same, are evidence that the intoxicating symptoms at their maximum will be similar. In other words, the symptoms of intoxication produced are no less when an intoxicating quantity of alcohol is taken in portions at intervals of 2 hours than when the same alcohol is drunk in one gulp. There is of course a postponement of the worst effect. At the beginning of these experiments it was

expected that, by giving the alcohol in portions, the rate of maximum accumulation after the third portion would be similar to the rate of absorption of the first portion, and therefore less intoxication might result. This has not proved to be the case except when the interval between the drinks is 3 hours or longer. With intervals of 2 hours or less the absorption of alcohol in one drink is stimulated by the absorption of the fluid of the previous drink. The increasing amount of alcohol in the blood accumulating at an increased rate brings about maximum intoxicating symptoms. When the interval is 3 hours or longer the absorption of the fluid of the first drink no longer stimulates the absorption of alcohol in the second drink, and a slower accumulation of alcohol in the blood takes place.

These results may at least be partially explained by later experiments in which the effect of drinking water on the subsequent absorption of alcohol was determined. It will be seen that, after water has been absorbed from an empty alimentary canal, it brings about such a state of affairs that alcohol is more rapidly absorbed than normally, and that this influence persists for 4 hours after the water has been drunk and possibly longer. In these experiments, however, the stimulation to absorption by the alcoholic solution was only obvious for 2 hours, and when the interval was 3 hours the second lot of alcohol was more slowly absorbed. Probably the difference between these results and those of the experiments with water depends on the different amount of fluid consumed in the different series. In the water experiments 500 c.c. were drunk, whereas in these experiments the greatest quantity of fluid taken at any period was never more than 125 c.c. The effect of the smaller quantity of fluid would probably disappear more rapidly than that produced by a larger quantity. It would appear probable that, if the experiments were repeated with more dilute fluids, e.g. beer, the intervals would have to be considerably longer than 3 hours if it were desired to do away with the stimulating factor of previous drinks and, by altering the rate of absorption of alcohol into the blood-stream, to lessen the symptoms of intoxication.

Summary.

These results show that the amount of alcohol in the blood at its maximum and the rate of accumulation immediately before this point is practically the same, whether an intoxicating dose of alcohol is drunk in one portion or in three portions at 1 or 2 hours intervals. When the interval was 3 hours, then, in this particular group of experiments, both the maximum point and the rate of accumulation were depressed.

VI. The Effect of Dilution.

The relative intoxicating values of strong and weak alcoholic solutions demanded investigation, and some of the results obtained in respect of the entry of alcohol into the blood when solutions of different strengths were taken will now be described. Fig. IV is a representative result of experiments on one dog.

In Curve A 40 c.c. of alcohol were given in a 20 per cent. strength.
" B 40 " " " " 5 " "
" C 30 " " " " 20 " "
" D 30 " " " " 5 " "

From the point of view of dilution, therefore, A and B are comparable, similarly C and D. It is evident that, whereas there is a distinct difference between A and B, there is but little between C and D. The maximum concentration in the blood in B does not approach the maximum concentration of A, and altogether there is throughout the period of the experiment, less alcoholic concentration in the blood when the alcohol was taken in the dilute form.

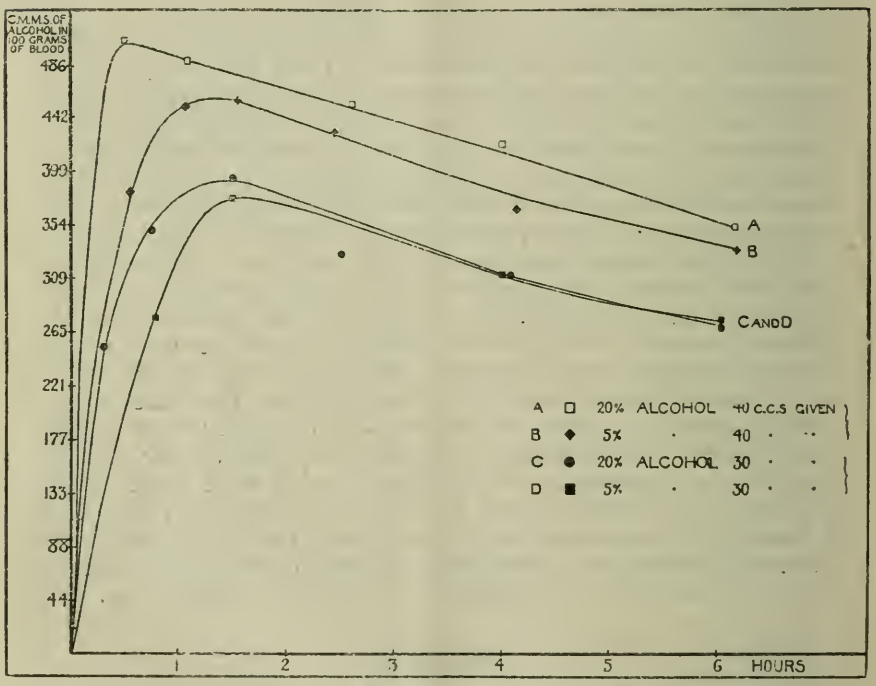

FIGURE IV.

It may be well to point out that the time element so far as drinking was concerned plays practically no part in the experiments. That is to say, even in experiment B, where it was necessary to give 800 c.c. of fluid, this was all placed in the stomach in the course of 3 or 4 minutes. The differences therefore in Curves A and B are entirely due to the different rates of absorption of strong and weak alcohol solutions when all the alcohol was present in the alimentary canal in each case. Stronger solutions of alcohol were also tried, but were not continued because they tended to irritate the stomach and cause vomiting, whereas weaker solutions than 5 per cent. were not practicable because of the difficulty of getting a larger bulk of fluid into the stomach within a few minutes.

The intoxicating symptoms produced by the weak and strong solutions were as might be expected from the curves. That is to say, in each case the dilute fluids produced less intoxication than the strong fluids containing corresponding amounts of alcohol. Whereas, however, there was a pronounced difference in the dog's condition in Curves A and B respectively, the difference was slight between C and D. This fact is the general rule, viz. that the greater the amount of alcohol taken, the greater is the difference between the intoxication symptoms and the blood alcohol when strong and dilute solutions are drunk. It is difficult to suggest a satisfactory explanation of this fact, but, speaking in general terms, it is probable that drinking a large bulk of fluid containing much diluted alcohol causes an increase in the general body fluids and a corresponding diminution in concentration of the alcohol present in the tissues and tissue fluids. With the elimination of this fluid through the kidneys and a restoration of the previous balance, it would be expected, unless, indeed, there is also an increased excretion of alcohol through the kidneys at the same time, that the alcohol present in the blood would ultimately be the same in whatever form of dilution strong and dilute solutions of alcohol were drunk. These experiments further show that this period of equality would only occur after the alcohol in the blood had passed its maximum and the worst symptoms of intoxication had passed off.

As for the slower rate of absorption of alcohol from the more dilute solutions, this can be easily understood. To get a concentration of x alcohol in the blood it would be necessary to absorb y c.c. of a 20 per cent. solution from the alimentary canal. To get the same concentration x after drinking a 5 per cent. alcohol solution, the alimentary canal would have to absorb $4y$ c.c. of solution. The difficulty of doing this in the short time that it takes to reach a maximum when a 20 per cent. alcohol solution is drunk, i. e. about 45 minutes, is obvious. This difficulty of arriving at the necessary maximum would be progressively greater with more dilute solutions than 5 per cent.

It is true of course that, in comparing 20 per cent. and 5 per cent. solutions of alcohol, the alcohol in the former might well have an inhibitory effect on absorption, so that the difference in time between the absorption of 1 vol. of 20 per cent. and 4 vols. of 5 per cent. might not be so great as 4 to 1. If, however, a comparison were made between a 5 per cent. and a 3 per cent. solution of alcohol, it is probable that a greater difference in the relative rates of alcohol absorption would be found, as the inhibitory effect of the alcohol would be small in both cases, and this difference would depend only on the relative power of absorbing proportions of water in the ratio 3 : 5.

Summary.

Comparing a 20 per cent. with a 5 per cent. solution of alcohol, when the same amounts of alcohol are drunk, the alcohol of the dilute solution is absorbed more slowly and attains a lower maximum in the blood than that of the strong solution. The difference is small when small quantities of alcohol are consumed, but becomes greater as the amount of alcohol increases.

VII. The Absorption of Alcohol in Different Beverages.

From the results obtained with dilute and strong solutions of alcohol, it might be expected that there would be some difference between the effect of spirits and beer. This is the case as can be seen in Fig. V.

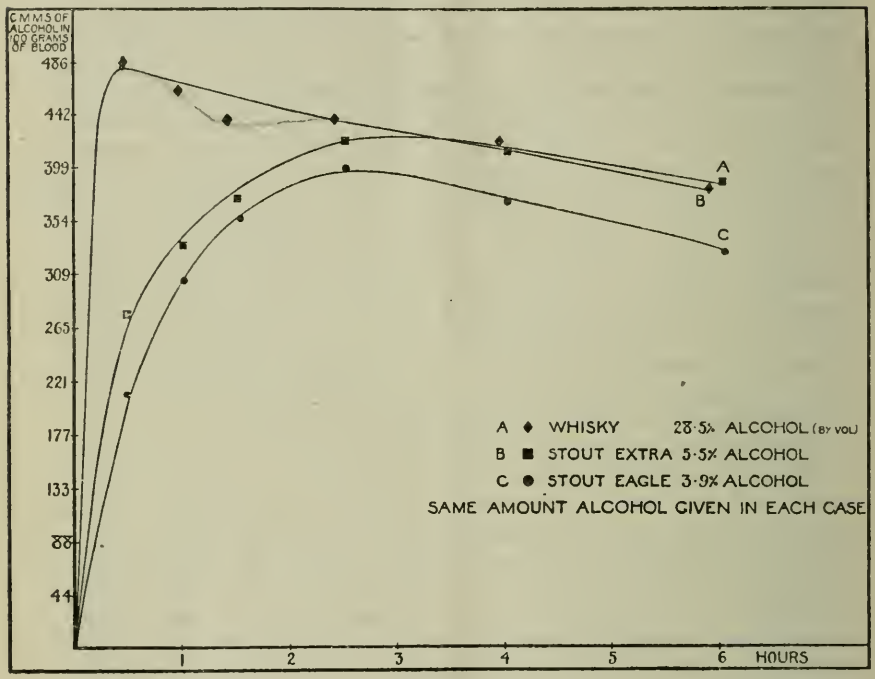

Figure V.

In Curve A 174 c.c. of whisky (28·5 per cent. alcohol by volume) were given.
In Curve B 910 c.c. of stout I (5·5 per cent. alcohol by volume) were given.
In Curve C 1,282 c.c. of stout II (3·9 per cent. alcohol by volume) were given.

In each experiment 50 c.c. of alcohol were given. The results obtained were strikingly different, the rate of absorption of the alcohol of the whisky being much greater and the maximum concentration in the blood being higher than in the stout experiments. Similarly, the weaker stout C (3·9 per cent.) produced lower alcohol in the blood throughout than stout B (5·5 per cent.). So marked was the difference in the intoxicating symptoms and the alcohol of the blood in the whisky and stout experiments respectively, that it appeared probable that some factor other than that of dilution was playing a part. In order to determine whether this was the case, the experiments detailed in Fig. VI were made. In these experiments, the whisky was diluted down to the strength

of the stout so that each contained 5·5 per cent. alcohol by volume. There is but little difference in the points of maximum concentration of alcohol in the blood in Curves A and B (Fig. VI), but there is a considerable difference between the rates of absorption of alcohol into the blood-stream in the two cases. In the case of the

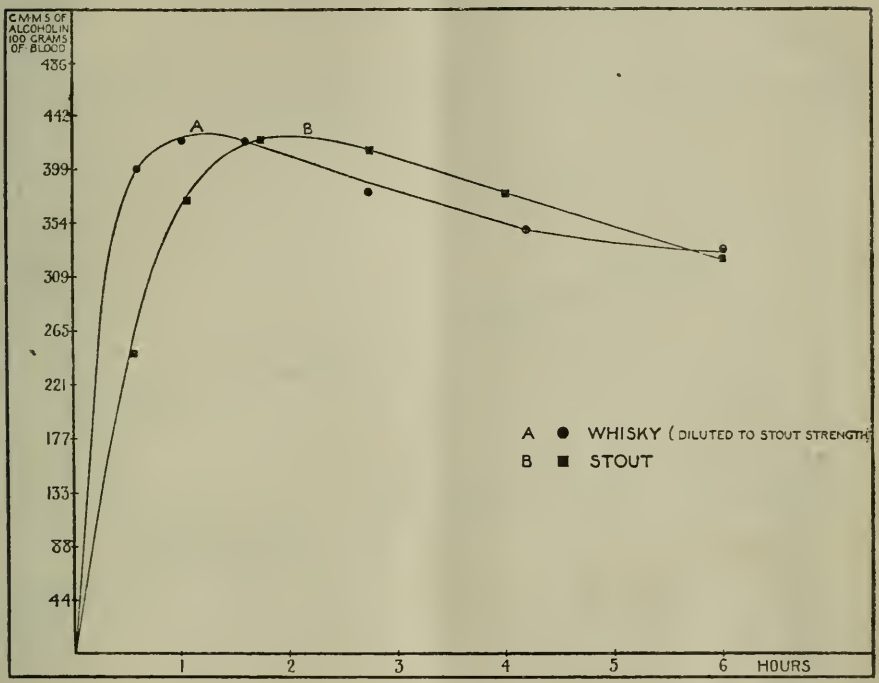

FIGURE VI.

diluted whisky the maximum concentration was reached $1\frac{1}{4}$ hours after the experiment started, in the case of the stout the maximum was only reached after 2 hours. It appears, therefore, that either whisky contains something which hastens alcoholic absorption or, what is more probable, that stout contains something which tends to delay absorption. It may be further remarked that, although the maximum amount of alcohol attained in each experiment was almost the same after the diluted whisky and the stout, it is undoubted that the symptoms of intoxication were more marked when the alcohol was more rapidly absorbed, i. e. in the case of the diluted whisky. What the component of the stout is which is capable of inhibiting the absorption of alcohol cannot be stated. It seemed possible that the substance conferring upon stout its colloidal nature was responsible, and, in order to determine this, 3 per cent. gum arabic was added to a solution of alcohol and the rate of absorption was compared to a solution of alcohol of similar strength without gum. Fig. VII shows that the gum in this experiment had no effect on the rate of absorption of alcohol. Similar experiments were made with starch as the colloid, but the results again were negative.

Summary.

The alcohol in stout is absorbed more slowly, and reaches a lower maximum in the blood than that of whisky. This is due to two conditions:

(1) The dilution of the alcohol in stout as compared with whisky.

(2) Stout contains something which inhibits absorption of its alcohol.

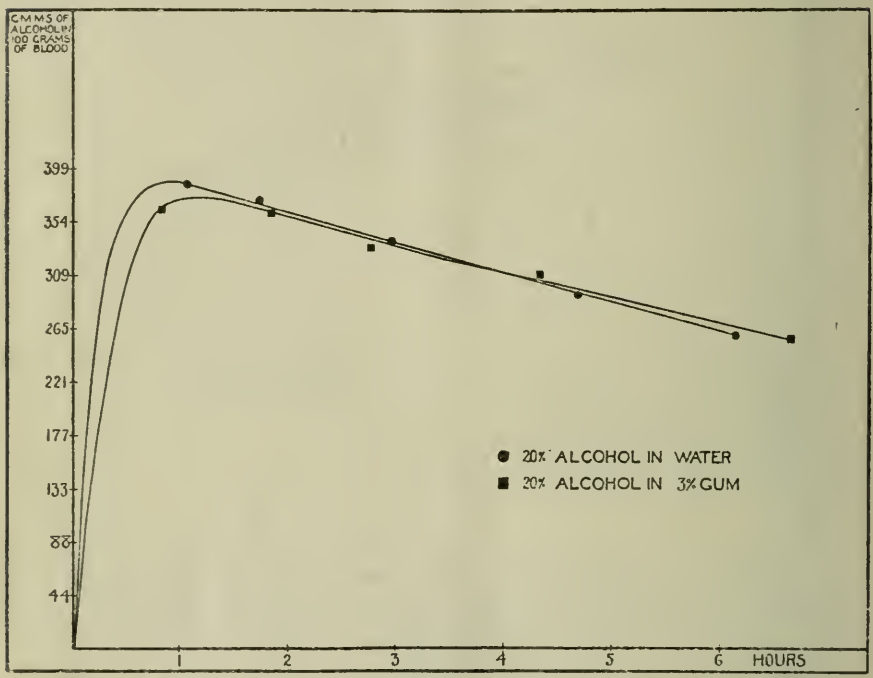

FIGURE VII.

VIII. THE EFFECT OF FOOD IN THE ALIMENTARY CANAL ON THE ABSORPTION OF ALCOHOL.

(*a*) *Bread and Milk.*

The effect of a meal of bread and milk on the absorption of alcohol is seen in Fig. VIII, which is typical of similar experiments made on the different dogs. The effect of eating such a meal is most marked when it is eaten less than 2 or 3 hours before the alcohol. With the lengthening of this period the curves more closely approximate to that of the control condition where no food has been taken for 20 hours. It will be noted that the portion of the curve most affected is that recording the first 3 hours of the experiment. During this period the curve is more flattened, so that not only is the maximum concentration of alcohol in the blood much lower than in the control curve, but also the rate of absorption is slower. As would be expected, therefore, the

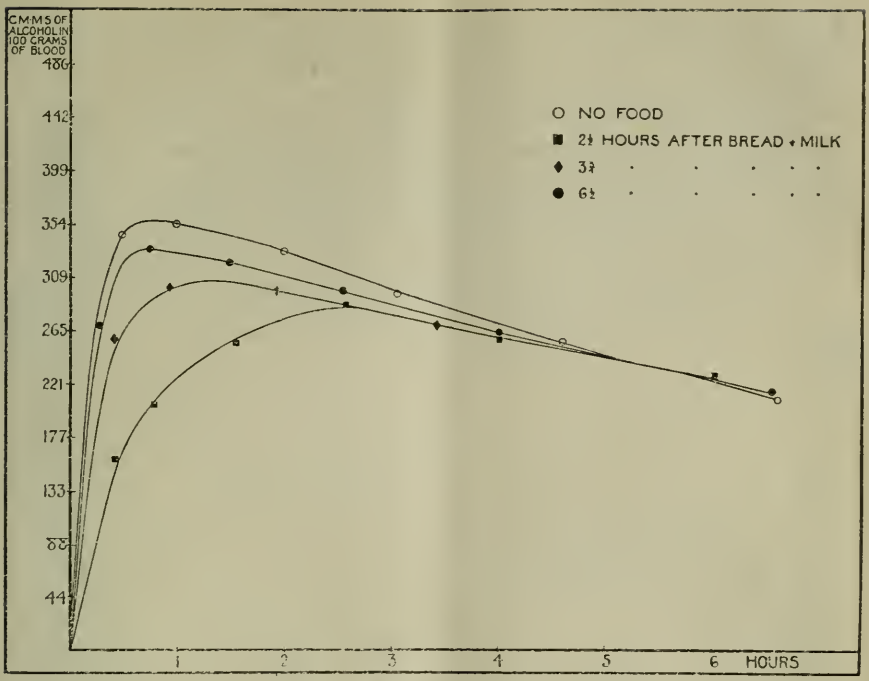

FIGURE VIII.

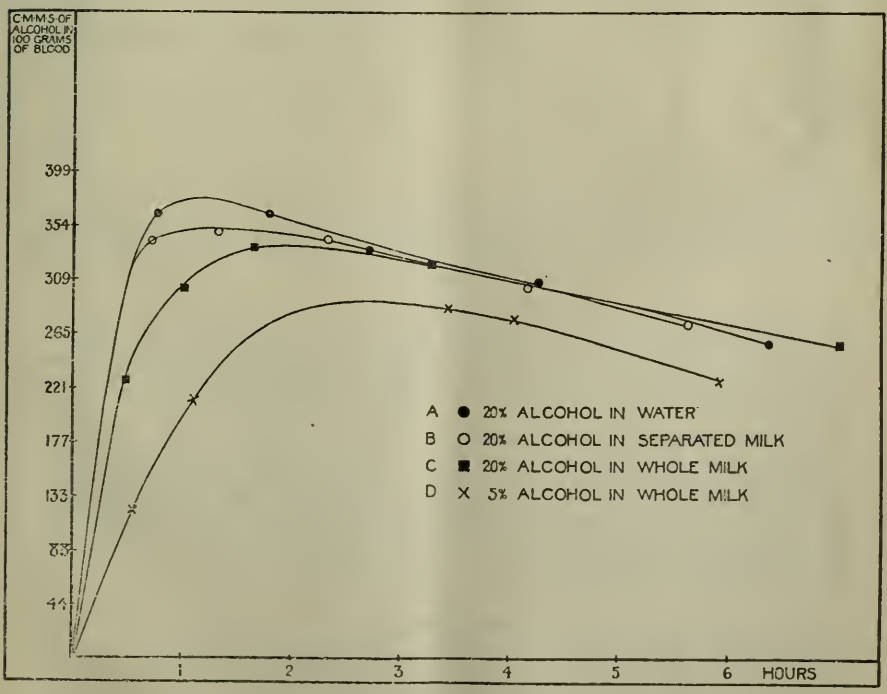

FIGURE IX.

period of maximum intoxication is very greatly reduced by a meal of bread and milk taken before the alcohol. It seemed likely that the effective part of the substances eaten was the milk, and this proved to be the case.

The inhibitory action of milk on the absorption of alcohol from the alimentary canal can also be obtained when the milk is added to the alcohol, and even when only small quantities of milk are used. Fig. IX shows this point. In Curve C 120 c.c. of milk were added to the alcohol, so that the total volume of fluid imbibed was 150 c.c.; in Curve B the same amount of milk was deprived of fat by a separating process before being added to the alcohol.

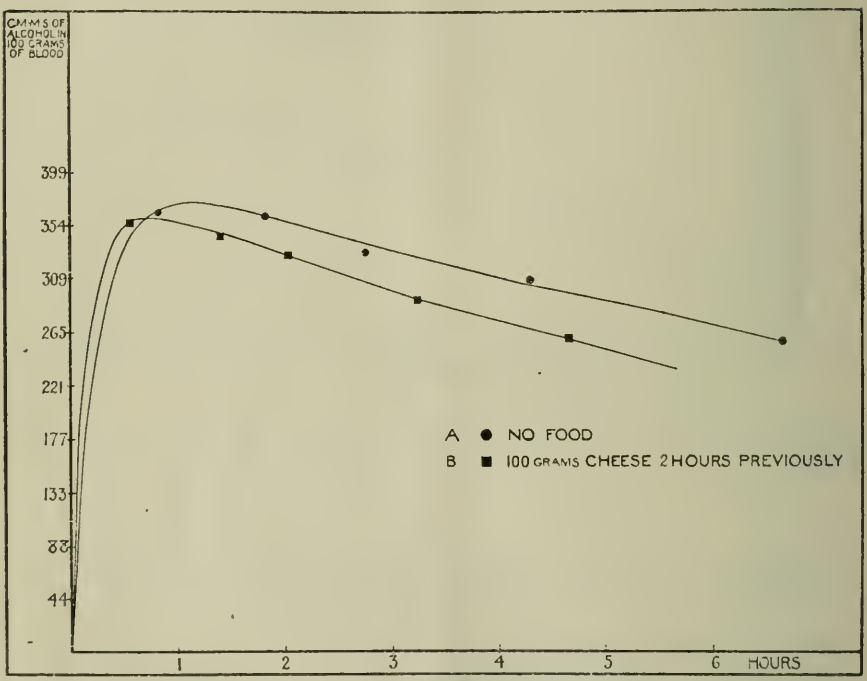

FIGURE X.

In each case there is a depressant effect produced by the milk. The whole milk was more effective than the separated milk. This point indicates that the milk fat plays an important part in this action.

In Curve D 560 c.c. of whole milk were added to the alcohol, so that in addition to its own action the element of dilution was also introduced into the experiment. It is therefore not surprising that this curve should be so relatively flattened. The reduction in the intoxication caused by adding a large quantity of milk to the alcohol is very striking.

(*b*) *Cheese.*

In view of the effect of milk it was thought desirable to see if cheese had a similar action in altering the curve of absorption

and lowering intoxication. The type of cheese used cannot be stated, but it was an ordinary brand procurable in these times. It may therefore have contained little or no fat. The result of eating 100 grammes of this cheese 2 hours before the alcohol was taken is seen in Fig. X. The cheese had little or no influence on the rate of absorption, but brought about a slight lowering in the maximum concentration. It may be, therefore, that a small part of the milk effect may be obtained with cheese, but by no means the whole effect.

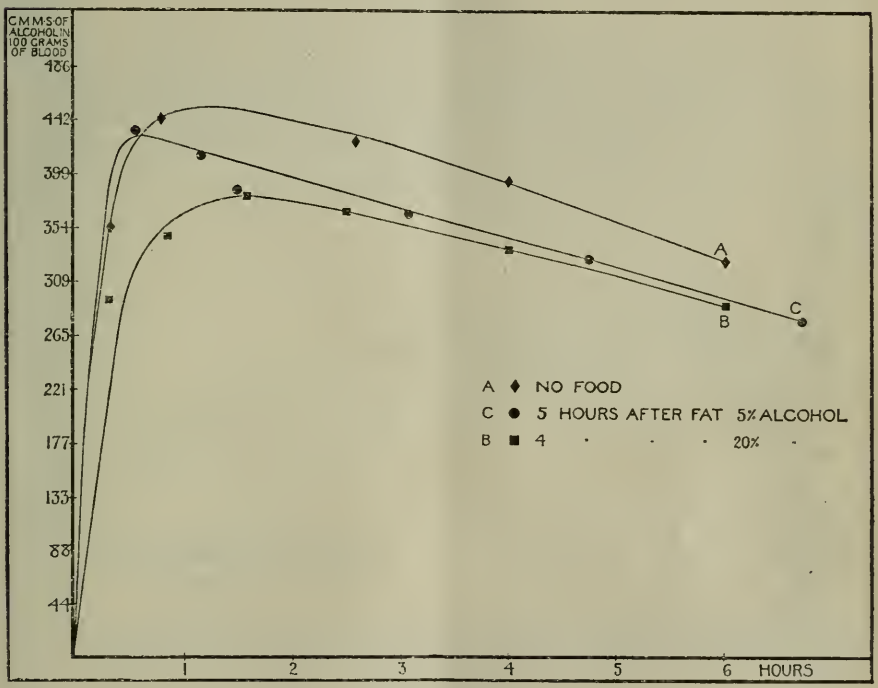

FIGURE XI.

(c) Fat.

The effect of eating fat before alcohol is shown in Fig. XI. Curve A is the control (no food) curve obtained after giving 50 c.c. in a 20 per cent. solution. Curve B was obtained after giving 50 c.c. of alcohol in a 20 per cent. solution following 100 grammes of suet eaten 4 hours previously. In Curve C the same amount of alcohol was given in a more dilute (5 per cent.) form also following a meal of fat. It will be observed that in the case of the 20 per cent. solution of alcohol, the rate of absorption is less and the maximum point of alcohol concentration in the blood depressed by the fat. When the dilute solution of alcohol was given, no depression of the rate of absorption was apparent, and, in fact, the absorption was rather more rapid than in the experiment without food. In view of the action of milk fat seen above it is probable that lower melting-

point fats, such as linseed or olive oils, would have produced more emphatic results.

It appears, then, that whereas fat has a depressing effect on the absorption of a 20 per cent. solution of alcohol, it has no such effect on a 5 per cent. solution. The explanation of this may be that the fat enters into a physical relation with the stronger solution, and so inhibits the absorption. With a 5 per cent. solution probably no such physical combination is possible, and the rate of absorption is unaffected.

(*d*) *Meat.*

The effect of eating meat prior to the taking of alcohol can be seen in Fig. XII. A half-pound of minced, lean beef was eaten by the dog 2 hours before receiving 250 c.c. of 20 per cent. alcohol. In the control experiment the same amount of alcohol was taken

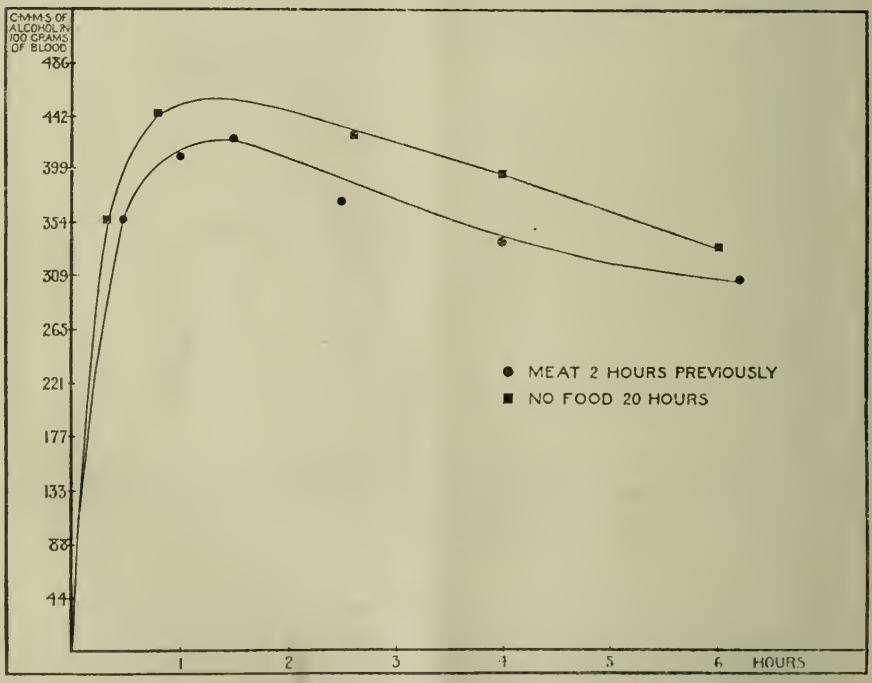

FIGURE XII.

when the stomach was empty. The presence of the meat depressed the rate of absorption and the maximum concentration of alcohol in the blood. The depressing effect is not so large as that possessed by milk.

Summary.

(1) Milk is the most effective food-stuff for delaying absorption of alcohol into the blood. It is almost equally effective whether mixed with the alcohol or drunk 2 hours before the alcohol. Its

action is quite independent of the dilution factor, although dilution with milk naturally acts in the same way as dilution with water.

(2) Cheese (war brand) had but little effect on the absorption of alcohol. The effect of meat was also small.

(3) Fat inhibits absorption of alcohol to some extent, and more especially that of stronger solutions (20 per cent.). The fat of milk is undoubtedly responsible for some of the inhibitory effect of milk, but possibly not all.

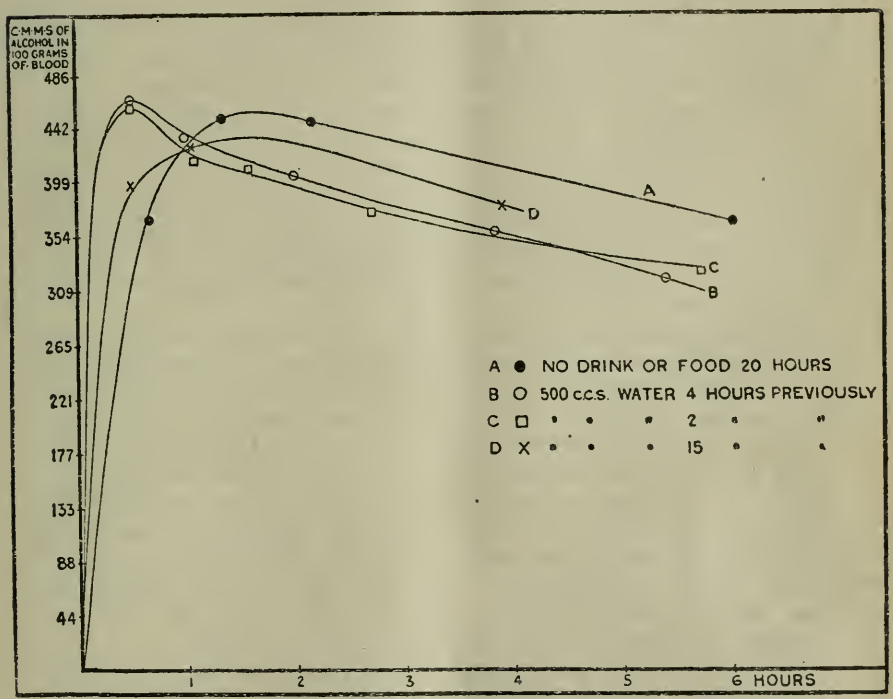

FIGURE XIII.

IX. THE EFFECT OF PREVIOUSLY DRINKING WATER ON THE ABSORPTION OF ALCOHOL.

It would be expected that the question of thirst as it involves absorption of alcohol from the alimentary canal would be simple, and that the more thirsty the animal the more rapid would be the absorption of alcohol. To some extent this is undoubtedly true, but complicating factors may be introduced into the experiments which do away with the possibility of attaching any importance to the generalization. In reality this is not surprising, for any specific absorptive action of the alimentary canal associated with thirst can only be brought about through a certain physiological condition of the intestine. If this condition could also be assured by the action of certain chemical substances on the mucous membrane of the alimentary canal, then rapid absorption would take place independently of thirst. If, further, it should happen that water is

a suitable substance for bringing about this specific condition, a more rapid absorption of alcohol in a dog after drinking water than in the same animal when thirsty might result. In these researches water has proved to be the best stimulus to absorption of all the substances investigated, so that we have the paradox of the most rapid absorption of alcoholic solutions taking place in animals the least thirsty. To place an alcoholic solution into the stomach immediately after drinking water would of course only result in the dilution of the alcohol, and the ordinary retardation of absorption associated with dilution. If, however, time is given to allow the water to be removed by absorption, say an interval of 2 hours, the alcohol will be very rapidly absorbed, because the water originally drunk has a certain stimulating action on the intestine.

This stimulating effect of water on alcohol absorption is well shown in Fig. XIII. In all experiments the water was withdrawn at 2 p.m. on the day prior to the experiment. In Curve C the dog drank 500 c.c. of water 2 hours before the administration of alcohol, and in Curve B the interval was 4 hours. In spite of this quenching of its thirst it will be seen that the alcohol was very rapidly absorbed, more rapidly indeed than when the dog got no water to drink (Curve A).

The same effect can be seen in Fig. III, described earlier, where alcoholic solutions were given at varying intervals. In such experiments the first drink of fluid brought about a more rapid absorption of subsequent drinks so long as the interval was not longer than 3 hours. After this time the effect of the previous fluid had apparently worn off, and the next solution of alcohol was more slowly absorbed. It would be well to point out here that the intervals mentioned only apply to these particular experiments, and that, whereas such results can undoubtedly be extended to man in a general way, corresponding data will have to be specifically obtained in man by similar experiments before the practical importance of the phenomenon can be fully appreciated.

To return to the theoretical side of the question, the stimulating effect of water on the absorption of alcohol from the alimentary canal may be of greater practical importance from a general physiological point of view than has been previously thought. The work of Pawlow[1] has made us familiar with the fact that water has a stimulating effect on the secretion of the gastric juice, probably in consequence of its power to liberate gastric secretin from the pyloric end of the stomach. In doing this it further augments the pancreatic and probably other secretions of the alimentary canal. Fowler and Hawk[2] have further shown that copious draughts of water increase the digestion and absorption of food-stuffs, and explained this by assuming that the increased secretions of digestive juices were responsible for a better reduction of the food-stuffs eaten to a form suitable for absorption. Since alcohol requires no digestion for absorption into the blood-stream, some other factor must be introduced to explain the stimulating effect of water, and it seems

[1] Pawlow and Thompson, *The Work of the Digestive Glands*, London; Griffin, 1910, 112.

[2] Fowler and Hawk, *J. Exper. M.*, N.Y., 1910, 12, 388.

probable that, in addition to its effect on the digestive juices, water has a specific stimulating effect on the cells of the intestinal mucous membrane responsible for absorption. The fact that the water effect continues even after 4 hours, suggests that its action may be due to a washing away from the walls of the alimentary canal of some substance normally inhibiting absorption. If, instead of water, milk be given before the alcohol, quite the opposite effect is produced and alcoholic absorption is greatly retarded. This is seen in Fig. XIV. In Curve C, 450 c.c. of milk was drunk 2 hours

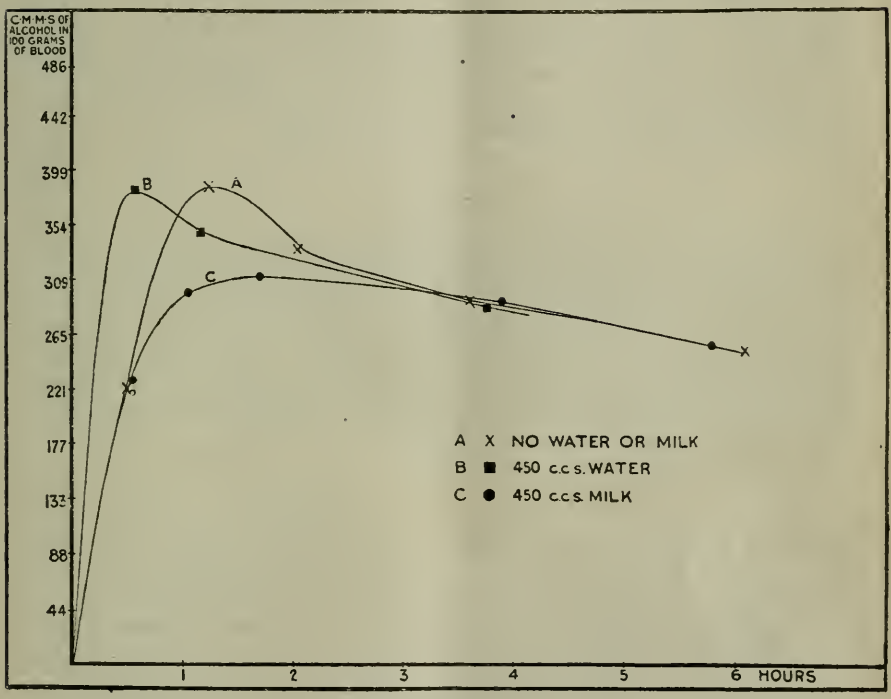

FIGURE XIV.

before the alcohol was taken. In Curve B, 450 c.c. of water was given, and in Curve A no food or fluid was allowed. The most rapid absorption is seen in Curve B, after water; the slowest in Curve C, after milk. It can be readily understood how different is the intoxication produced in the same animal by the same amount of alcohol under the different conditions.

These facts demonstrate how difficult it is to relate the absorption of alcohol to thirst, since the latter is completely dominated by certain conditions of the alimentary canal. If this can be eliminated by withholding fluid and food for many hours, then it is probable that the thirst factor may be of some importance, so that the more thirsty the animal the more rapid will be the absorption. Since, however, any animal would be thirsty to some degree after water has been withheld for the requisite number of hours, say 4 hours, the differences produced by different degrees of thirst would not be as pronounced as the differences already discussed.

The interpretation of these Curves in terms of intoxication will be discussed later.

Another point worthy of comment is the more rapid descent of Curves C and B (Fig. XIII), i.e. after the water has been drunk. This is probably due to the retention of the fluid previously drunk bringing about a greater dilution of the alcohol in the tissue fluids and blood. It appears as if the alcohol were rushed so rapidly into the blood that it had not time to get distributed in a normal way throughout the tissues of the body. After reaching a maximum the alcohol in the blood in Curves C and B is got rid of and distributed to other parts, bringing about an unnaturally rapid diminution. This is further exaggerated by the increased volume of fluid retained from the previously drunk water, so that the concentration of alcohol in the blood is alternately higher and lower than that existing when no water is drunk.

Summary.

The effect of thirst on the absorption of alcohol appears to be dominated by the condition of the alimentary canal. Water acts as the best stimulant to absorption so far discovered in these experiments, and a drink of water some hours before the alcohol causes a more rapid absorption of the latter. These results are in harmony with the previously observed fact that the fluid of a first drink of an alcoholic beverage can act as a stimulus to the absorption of the alcohol of a second drink.

X. The Effects of the Various Conditions on Intoxication.

It may be well to use the subject of intoxication as the peg upon which to hang and bring together the more salient facts described in the foregoing experiments. As I have pointed out in the beginning of this work, it is but a frail peg because of the impossibility in such experiments on dogs of measuring the degree of intoxication. It is true that there are certain definite signs of intoxication which might with great difficulty be classified in a certain order. Such signs, for instance, as scraping the toe-nails on the floor in walking, weakness in the hind legs as is evident on standing still, a rolling gait, stumbling, difficulty of getting on to feet after falling, and complete inability to walk, and collapse, are a series which act as a rough guide. They are, however, not sufficiently exact to bring into correlation with accurate alcohol estimations. Unfortunately also such symptoms usually appear in the first 2 hours of intoxication, and, after this period, except for considerable lethargy and general lack of interest in its surroundings, the dog may appear normal. This means that only the grosser kinds of inco-ordination are evident, and that, at a period when the animal must be considerably affected by the alcohol, which is at a high concentration in the blood, there is no reliable indication of the abnormality of the nervous system, much less can a true judgement be made of the intensity of the intoxication.

In dogs, therefore, the only symptoms of intoxication obvious are those mainly connected with balance and movement of the legs. In man inco-ordination is only a small part of the effect of alcohol, and yet it forms a more important part of the symptoms than in the dog. It has been pointed out that the hind legs of a dog are the first to show weakness, and that it is this which makes it more difficult for a dog to stand still than to walk when intoxicated. In walking, the weakness of the hind legs is compensated for by the front legs and the muscles of the other parts, and collapse prevented. Now in man the whole support of the body depends on the legs, and the base of the standing man is relatively much smaller than that of the dog. Consequently balance is a more difficult matter in an intoxicated man, and therefore unsteadiness is a more predominant feature in the complete picture. It can be readily understood how small is the part played by inco-ordination of the legs in the intoxication of dogs, and how difficult it is to apply such meagre results to man, especially as there is no means of judging all the other activities of the dog's brain and how they are influenced by intoxication. It is essential, therefore, to remember that the statements made in this section on intoxication demand confirmation at the hands of one who has reliable methods of estimating the intensity of intoxication. It is further necessary that these tests be directly applied to man, partly because it is easier, and more particularly because the question of alcoholic intoxication in man is the subject at issue.[1]

My justification for labouring this point is that I must confess to having been misled as to the real nature of the symptoms of intoxication and its relation to blood-alcohol by judging only of the dog's condition, and to have had my ideas altered by watching similar experiments in man which will be reported later. The rapid disappearance of inco-ordination in the early period of the experiments on dogs led me to believe that the recovery from intoxication was rapid. This I no longer believe, although, undoubtedly, improvement takes place immediately after the alcohol has reached a maximum in the blood.

I will now discuss the question as to how intoxication is influenced by various factors as it appeared in this experimental work.

(*a*) *The Amount of Alcohol drunk.*

It has already been seen in Fig. I that the amount of alcohol in the blood of a single animal is, other conditions being equal, proportional at its maximum to the amount drunk. This statement, however, does not appear to hold with any accuracy for small quantities of alcohol: in these experiments it does not hold when the alcohol consumed is 1·7 c.c. per kilo or less. With these smaller quantities of alcohol there is less in the blood than would be expected.

[1] Since these results were reported to the Scientific Committee of the Central Control Board (Liquor Traffic) work on these lines has been carried out by Dr. H. M. Vernon and Dr. Sullivan.

As the alcohol in the blood increases the symptoms of intoxication also increase. With dogs, however, a condition of affairs can be seen which is striking, but I rather doubt whether a similar change occurs in man. This is the relatively small increase in the alcohol of the blood which divides a dog slightly intoxicated from one helplessly intoxicated. In the case of the large brown dog, when the concentration of alcohol in the blood was 446 cm. per 100 grammes of blood the dog appeared slightly intoxicated, rolled a little on walking, could not stand steadily without support, and moved in a lethargic manner. When the concentration was raised to 468 cm. per 100 grammes the dog was profoundly intoxicated, could not get on to its feet even when helped, and for a period of time was in a collapsed state. The mild intoxication in this dog was produced by 50 c.c. of alcohol, and the intense intoxication by 55 c.c. The dramatic difference in the picture of intoxication produced by a small increase in alcohol is, I think, only striking because of the crudity of the indication of intoxication. Although the additional 5 c.c. of alcohol is the 'last straw', so to speak, the mechanism of co-ordination of walking is undoubtedly greatly influenced by the smaller dose, although the manifestation of such an influence is not so apparent because of the extraordinary strength of the entire mechanism. When it appears disarranged or affected as by the 50 c.c. of alcohol, it really is near the breaking-point. No doubt if there were means of measuring other actions of the nervous system of the dog, a gradual alteration in function as the alcohol in the blood increased would be found, and not the change to sudden collapse seen in the example discussed. In the experiments on men that I have performed I have seen no indication that a small increase in the alcohol of the blood synchronises with a sudden transformation of the intoxication symptoms. The whole picture, in fact, has appeared to me as a gradual development of symptoms with increasing alcohol.

A dog begins to show signs of intoxication when the alcohol of the blood reaches about 354 cm. per 100 grammes of blood. At this stage it will probably hit its hind toes against the floor on walking. Its movements will be slower and after a period of excitement its interest in external conditions will be less than usual. This only applies to the ascending portion of the curve. It has already been stated that the symptoms decline after the maximum of the alcohol in the blood has been reached. When the alcohol has declined again 354 cm. the dog will probably appear almost normal, and will certainly be less intoxicated than at the corresponding point on the ascent of the curve. The explanation of this may be along several lines.

(1) The nervous system is probably more affected by the sudden attack of the alcohol recorded by the upgrade course of the curve.

(2) The nervous system may re-learn to co-ordinate its activities after being under the alcoholic influence.

There is evidence that both these factors are involved in the course of a period of intoxication and both will be mentioned in due course.

(b) *The Rate of Absorption of Alcohol.*

It is difficult to differentiate between the effects of rate of absorption into the blood-stream and those due to its concentration, for a more rapid absorption is nearly always accompanied by a higher maximum. In Fig. XIII it will be seen that the curves of absorption after water (Curves B and C) are not only more rapid but their maximum point represents 464 cm. of alcohol in 100 grammes blood, while the corresponding number of Curve A, when the animal had had no food or water, is 453 cm. It was to be expected, therefore, that the animal in Curve B experiment would be more intoxicated than in Curve A. This was the case and the difference was great. It seemed possible that part, at least, of the increased symptoms might be due to a more rapid absorption of alcohol involving a more sudden attack on the nervous system. In order to get definite information on this point it is essential to compare a dog in two conditions, when the rate of absorption alters but the maximum point of concentration in both cases is the same. Such an instance is seen in Fig. VI, where a dog has taken stout, as in Curve B, and whisky diluted to the stout strength, as in Curve A. The rate of absorption of alcohol differs in these experiments, the maximum concentration in each case reaching 425 cm. per 100 grammes of blood. It seemed to me in this case and in similar experiments on another dog that the animals were undoubtedly more intoxicated after drinking the more rapidly absorbed dilute whisky. The period of more intense intoxication was but brief and diminished with the reduction of alcohol in the blood. In some cases of more rapid absorption, the rate of diminution of alcohol in the blood was also increased, so that the dog was intensely intoxicated for a short time, say 10–15 minutes, and then made a surprisingly rapid recovery (see Fig. XIII).

Previous work has all centred round the relation of intoxication to concentration of blood-alcohol, so that any other factor such as the one under discussion seemed worthy of mention. A crude kind of explanation of the increased inco-ordination of the grosser type produced by more rapid absorption of alcohol which might be suggested is that, when the attack of the alcohol on the nervous system is slow, the nerve-cells have the opportunity to re-arrange their interactions and call in additional nerve-cells to meet the new situation, but that, when the attack is more sudden, the cells are taken completely unaware and the system is suddenly knocked out of gear. That the nervous system can re-learn to co-ordinate under the influence of alcohol seems clear from the difference between a dog which has been held down on the table after receiving its requisite dose of alcohol until the time of maximum concentration, and the same dog which has been allowed to run about. In the latter case the dog re-learns as it runs, but, in the former, when released after being held down, it is often quite helpless for some minutes. After lying helpless it will pass through a period of experimental effort, endeavouring to rise, succeeding eventually only to fall down again and again, until finally an adequate mechanism of balance and co-ordination is called into play.

(c) *The Effect of Dilution.*

It has been seen that the effect of diluting alcoholic solutions (Fig. IV) is twofold: (1) the maximum concentration of alcohol in the blood is lowered, (2) the rate of absorption is depressed. It was further shown that the difference between the results obtained with strong and weak solutions became more marked the greater the quantity of alcohol drunk. In terms of intoxication, these results can be interpreted as follows: the greater the quantity of alcohol consumed. the greater is the difference in the intoxication produced by strong and weak solutions. Also, the more tolerant a man is of alcohol, that is. the higher the point the alcohol has to attain in the blood before desired symptoms of intoxication are produced, the more difficult will it be to produce these symptoms by dilute beverages. It was further seen that these results apply also to alcoholic beverages, e.g. whisky and stout, only that in this case another factor was apparently introduced, for the stout contained something which inhibited the absorption of alcohol. It was evident, for instance, that whisky diluted to stout strength was still more rapidly absorbed than stout. It ought to be more difficult to get drunk on stout containing 5·5 per cent. alcohol by volume than on a pure solution of alcohol of equal strength.

In Fig. V it was also seen that there was a considerable difference in the alcohol of the blood following the drinking of 5·5 per cent. and 3·9 per cent. stout. These facts have been discussed in a previous section; also the reason why the alcohol of the blood remains so much lower after drinking dilute beverages than after spirits has been discussed. It may be stated definitely that the differences in the intoxication produced by the various drinks are as characteristic and definite as are the blood-alcohol results. In the case of strong alcoholic solutions such as whisky, the symptoms come on more rapidly and are much more intense than with stout and other dilute solutions. No evidence, however, was obtained of there being any qualitative difference in the intoxicating symptoms produced by the different beverages.

In man, one factor bound up with the question of dilution must come into consideration which has been avoided purposely in these experiments. This factor is the ability to drink, during a specified period, an amount of fluid containing the quantity of alcohol requisite for intoxication. In normal times, with abundance of strong beer, this may not be of importance, but, at present, when Government ale containing only a small percentage of alcohol is the main drink, it must be somewhat difficult in the periods during which public-houses are open to drink the volume of fluid necessary to produce intoxication without bringing about vomiting. and incidently thereby avoiding intoxication. The consideration of this side of the question is, however, outside the scope of this paper. Here we have seen that, the greater the dilution of the fluid drunk, the lower is the alcohol concentration of the blood and the less rapid the absorption. The more diluted the beverage, therefore, the more alcohol has to be consumed to raise this substance in the blood to the requisite concentration for intoxication, and the more difficult is it to produce intoxication.

(*d*) *The Effects of Fluid and Food.*

We have seen that, on the whole, the presence of food in the alimentary canal inhibited the absorption of alcohol, so that a slower rate of accumulation of alcohol in the blood and a varying depression in the maximum concentration resulted when the stomach and intestines contained food. Substances varied considerably in their influence, so that whereas milk was the most active inhibitor, meat and cheese were the least. A hard fat like suet had an intermediate action between these substances, and, in addition, its effect was more obvious in connexion with strong than with weak alcoholic solutions.

One factor can be at once dealt with and eliminated. It might be thought that food-stuffs absorbed into the general circulation would play some part in aiding the defence of the body against alcohol. For instance, for many hours after a meal of fat, a considerable amount of this substance remains in the blood and other tissues, and the question arises as to whether this or other circulating food-material affects the course of intoxication independently of the alimentary canal. My observations lead me to believe that they do not, and that the interpretation of the curve of alcohol in the blood in terms of intoxication is the same in their absence as in their presence. This statement is made with some reserve and is subject to revision on further examination by more accurate methods. It is, of course, a most important point, for it might be possible to prevent intoxication or affect its development by food-stuffs, in a manner other than by altering the absorption of alcohol from the intestine. If, for instance, the alcohol could be fixed in the circulating fluids and its access to nerve-cells prevented, a step of considerable practical importance would have been achieved. The symptoms of intoxication are strikingly depressed by milk, but I consider this depression can be satisfactorily explained by the altered curve of alcohol in the blood without assuming any action of the milk digest products present in the tissue fluids and body generally. If 6 or 8 hours be allowed between the consumption of the milk and the alcohol, the symptoms developed are usually as great as when no food has been taken, although digestive products must be circulating in the blood-stream. Therefore I am inclined to believe that, even in the food experiments, the curves of alcohol in the blood can be interpreted in terms of intoxication in the same way as when no food is taken.

Undoubtedly a part of the effect of food depends on the question of dilution of the alcohol in the alimentary canal, but only a part. For instance the inhibiting action of milk is evident after an interval of 3 hours, when it is certain that the fluid portion of the milk will have been absorbed. Probably the fat of milk is of importance in this respect, in view of the results described above with separated milk. However, I do not consider the fat can explain the whole result, which for the time being must remain incompletely accounted for.

In contrast with the effect of food on the absorption of alcohol we have seen the curious and unexpected results obtained with water. When alcohol is taken immediately after water the results

can be explained as simply those following dilution. When, however, a few hours' interval is allowed for the absorption of water, then alcohol is absorbed at a record rate, much faster indeed than in the same animal when thirsty. Fig. XIII demonstrates this fact and incidentally shows that the disappearance of alcohol from the blood is more rapid than in the control animal which has not received water. The condition of intoxication follows these curves. That is to say, 2 to 4 hours after drinking 500 c.c. of water the intoxication produced by the alcohol may be very intense, but an equally striking fact is the rapidity with which the intensity of intoxication diminishes In such circumstances the dog may be more profoundly intoxicated 15 minutes after receiving the alcohol than the same dog, when no water has been drunk, 45 minutes after receiving the same amount of alcohol. On the other hand the recovery after water is much more rapid. No doubt the rapid recovery and the quicker descent of the alcohol curve after drinking abundant fluid can be associated with the retention of water in the body so that the total sum of body fluids is increased. In fact a condition of affairs arises such as has been met in the case of drinking a large volume of dilute 5 per cent. alcohol. In the above-described experiments 20 per cent. solutions of alcohol were taken by mouth. Thus we see that dilution of alcohol, and therefore an effect on intoxication, can be produced either directly in the intestine or indirectly in the body: the first by drinking dilute alcohol, the second by drinking alcohol some hours after water has been taken. The difference, however. between the effects on intoxication is that, whereas the first condition will alleviate the symptoms throughout, the second condition in the earlier periods of alcoholic absorption produces more intense intoxication than usual and the alleviation due to dilution follows this later. It is certainly most impressive to compare the relative intoxicating symptoms following a certain dose of alcohol in the same dog 2 hours after it has received respectively 500 c.c. of milk and 500 c.c. of water. In the first case the dog will probably show no sign of inco-ordination whatever, and in the second case will be quite incapable of standing or walking for some time.

(e) *The Relative Effects of Slow and Rapid Drinking.*

It has been stated that there is but little difference in the curves of alcohol absorption, whether a dog takes 250 c.c. of a 20 per cent. solution of alcohol at once or in four portions at 10 minutes intervals. In keeping with these facts the extent of intoxication was similar in both cases.

In other experiments (Fig. III) the intervals between the portions drunk were lengthened to 1, 2, and 3 hours. Naturally the shapes of the curves produced were altered, but, except in the case of the long interval of 3 hours, the maximum point of concentration was almost the same and the rate of accumulation of alcohol up to the maximum point identical, the rate becoming more rapid as the curves ascended. Whether the animal was given all the alcohol at once or in portions at intervals of 1 and 2 hours, therefore, the amount of intoxication at its worst was practically the

same, the only difference being that there was a delay in the development of symptoms corresponding to the delayed periods of drinking. When, however, the interval was extended to 3 hours, the maximum point attained was rather lower than in the foregoing experiments, and the rate of accumulation of alcohol in the body was relatively diminished after the second drink. The dog in this case was less intoxicated.

It may be well to point out that these results were obtained with a moderately strong solution of alcohol (i.e. 20 per cent.), and it is possible that different effects might be produced with more dilute drinks where the volume of fluid imbibed is greater, the time of absorption longer, and the dilution of alcohol in the blood owing to retained fluid more pronounced. Explanations of the facts have been offered in a previous part of this work, and here it only remains to say that, in order to alleviate symptoms of intoxication in dogs by drinking a definite quantity of alcohol in two or three portions rather than at once, the intervals must be long, probably a matter of 3 hours, and the longer the intervals the more obvious will be the difference in the condition of intoxication. Differences in intensity of intoxicating symptoms obtained by taking the same amount of alcohol in one or several drinks probably depend on the type of beverage drunk, and the intervals between the drinks.

Summary.

In this discussion of factors influencing intoxication, it is seen:

(1) That intoxication is related to the amount of alcohol in the blood and probably to the rate of accumulation in the blood.

(2) That dilute solutions of alcohol are less intoxicating than strong solutions containing the same amount of alcohol, the difference becoming more marked the greater the quantity of alcohol consumed and the greater the dilution.

(3) Food-stuffs inhibit intoxication in consequence of their action on the absorption of alcohol from the alimentary canal. The most effective food is milk, the action of which is dependent to some extent on its fat content.

(4) Water, after absorption, stimulates the absorption of alcohol, and thereby causes a rapid and intense intoxication from which recovery appears to be quicker than normal.

(5) Whisky is more intoxicating than stout, partly because of its greater concentration of alcohol, and partly because stout contains something which inhibits the absorption of alcohol to some extent.

(6) In order to obtain alleviation of symptoms of intoxication by splitting up an alcoholic beverage into two or three portions, the intervals between the drinks must be long, 3 or more hours, the time depending on the concentration of the fluid and the amount of alcohol contained therein. It is probable that the more dilute the beverage and the fewer the portions into which the drink is divided, the longer must be the interval between drinking in order to escape the maximum intoxicating symptoms.

XI. Alcohol as a Food.

Using the same method, that is to say, following up the alcohol content of the blood, some experiments were made to see if further insight could be obtained into the metabolic properties of alcohol. The results obtained in this investigation give no indication as to the fate of the alcohol as it disappears from the blood. On the other hand, they allow the subject of alcohol as a food to be approached from a different standpoint to that usually adopted, and, taken in conjunction with the researches of workers who have used other methods, they present a complementary picture which controls and in some cases extends present knowledge of this subject.

If we consider the large brown dog, it can be seen from the curves, e.g. Fig. II, that, after receiving 50 c.c. of alcohol, the blood was practically free from alcohol in 20 hours, i.e. at the rate of 2·5 c.c. per hour. The dog's weight was 13·5 kilograms, so that the rate of disappearance of alcohol was about 0·185 c c. per kilogram weight per hour. If this were completely oxidized it would supply 1·04 calories. I do not know what the total loss of heat was in this dog during the experiment, but it would probably be something of the order of 2·5 calories per kilogram weight per hour. The energy supplied by alcoholic oxidation would therefore be about 41 per cent. of the whole loss. In the absence of figures giving the total loss of heat this figure is only a rough estimate. Völtz and Dietrich[1] have shown that 42 per cent. of the total energy of metabolism of resting dogs was supplied by alcoholic oxidation in a 10 hours' experiment, and 35 per cent. in a 15 hours' experiment. However, the energy supplied to the dog in the above experiment, i.e. 1·04 per kilogram per hour, is much higher than that calculated by Völtz and Dietrich. Probably some part of the discrepancy can be accounted for by the fact that the dogs used by Völtz and Dietrich were at rest, whereas my dogs were able to run about a room during the experiment.

Similar results have been obtained in experiments made to determine the effect of alcohol on the respiratory quotient. For instance, Higgins[2] has made use of Rosemann's[3] formula, and thereby estimated that the oxidation of alcohol supplies the human body with 28 per cent. up to 40 per cent. of the total energy lost during the experiments.

Rosemann's formula is

$$Oa = \frac{O(q-qa)}{q-0{\cdot}667},$$

where Oa = oxygen consumed in burning alcohol.
O = total oxygen utilized.
q = respiratory quotient before the alcohol was given.
qa = „ „ after „ „ „
0·667 = „ „ for alcohol oxidation.

[1] Völtz u. Dietrich, *Biochem. Ztschr.*, Berl., 1915, 68, 118.
[2] Higgins, *J. Pharmakol. & Exper. Therap*, Balt., 1917, 9, 441.
[3] Rosemann, *Oppenheimers Handbuch d. Biochemie*, 1911, 4 (1), 423.

Using this formula the amount of oxygen used up in the oxidation of alcohol has been calculated, and this allows the percentage of the total energy supplied by alcoholic oxidation to be determined. Criticism of Rosemann's formula will be made later.

It has been previously pointed out in this paper that the rate of alcohol combustion is independent of the amount drunk, so that, whether the animal received a great or a small quantity of alcohol, the rate of oxidation remained approximately the same, and therefore the amount of energy in unit time supplied to the metabolism remained unchanged. Using the respiratory quotient method Higgins has come to a similar result. He found that the drop in the respiratory quotient produced by alcohol in resting men was the same whether 30 c.c. or 45 c.c. was drunk, so that the amount of oxygen used up by the alcohol in unit time was the same in spite of the varying amounts of alcohol imbibed. Now this conclusion is an important one, and places alcohol in a different category from other non-nitrogenous food-stuffs, for in these cases, at least with fats and carbohydrates, the evidence indicates that the effect on the metabolism distinctly varies with the amount consumed. The following figures[1] obtained by Gephart and Du Bois show the effect on the respiratory quotient of giving varying quantities of glucose to man:

Hours after food	1	2	3	4
100 grammes glucose	0·91	0·89	0·88	0·90
200 „ „	—	0·95	0·93	0·95

It is evident that more glucose is being oxidized when the large quantity is eaten, for the respiratory quotient rises considerably higher in the case of the 200 grammes experiment. It was further observed that 100 grammes of glucose caused an average increase of 9 per cent. in the heat production, and 200 grammes an increase of 12·5 per cent. during the 3 to 6 hours after ingestion. Fisher and Wishart,[2] working in Lusk's laboratory, found that the height of metabolism was about the same whether 50 or 75 grammes of glucose were taken by dogs, only in the latter case the effect was prolonged. Their curves, however, show that carbohydrate affected the respiratory quotient to a greater degree when the larger quantity was taken, as was seen above in the Gephart and Du Bois[3] results.

In the case of fat also, previous experimental work has shown that the metabolism is quantitatively affected by varying quantities. Forssner[4] has obtained the following results after giving varying quantities of olive oil to a man on a diet of sufficient caloric value (3,380 calories), but deficient in carbohydrate (160 grammes).

	Total acetone bodies	β-oxybutyric acid
No olive oil	5·11 grammes	3·69 grammes
40 grammes olive oil	9·16	7·22
60 „ „	9·96	8·08
80 „ „	11·80	9·52

[1] The following examples were taken from G. Lusk's book, *Science of Nutrition* (Saunders), 1917.

[2] Fisher and Wishart, *J. Biol. Chem.*, N.Y., 1912, 13, 49.

[3] Gephart and Du Bois, *Arch. Int. Med.*, Chicago, 1915, 15, 835.

[4] Forssner, *Skandin. Arch. f. Physiol.*, Leipz., 1910, 23, 1915.

These amounts were excreted between 11.0 p.m. and 10.0 a.m. of the following day. No doubt the increase in fat combustion would be more obvious with increase in amount ingested if a sufficiency of carbohydrate had been present.

Again, Magnus-Levy[1] obtained an increase of 10 per cent. in metabolism above the original basal level on giving a dog 140 grammes of bacon fat. When 320 grammes of the fat were eaten there was an increase of 19 per cent. in the metabolism between the 3rd and 6th hours. These results obtained with carbohydrates and fats indicate that there is a quantitative relation between the amount eaten and the effect on the metabolism, and we have further seen that no such relation as this holds in the case of alcohol, where the amount oxidized is apparently independent of the amount imbibed.

Rosemann's[2] formula given above was designed to afford information as to the amount of oxygen used up in the oxidation of alcohol over any specific time. From this it can be calculated at what rate the alcohol is being oxidized. The development of the formula depends on two points, (1) that as the result of drinking alcohol there is no increase in the total oxygen intake; (2) that the respiratory quotient for substances other than alcohol before and after its entry into the blood-stream remains the same: that is to say, the alcohol replaces carbohydrates and fats in the same proportion as was being oxidized prior to the alcohol being drunk. Now the first of these points is a fact, and the second is an assumption which seems to me to be incorrect. In Higgins's[3] respiratory quotient experiments it was shown that the higher the respiratory quotient the greater was the fall produced by alcohol.

The following table is a summary of results obtained in his respiratory quotient experiments, together with the amounts of alcohol oxidized per hour calculated on the basis of Rosemann's formula:

Average Respiratory Quotients following the giving of 30 c.c. Alcohol.

R. Q. before alcohol	R. Q. after alcohol	Drop due to alcohol	Calculation of percentage of total O_2 consumption caused by alcohol (Rosemann's formula)	Calculated amount of alcohol burned per hour
0·90	0·805	0·095	40 %	4·91 c.c.
0·85	0·795	0·055	28 %	3·68
0·80	0·775	0·025	20 %	2·75

We see that, according to the above calculations, the rate of combustion of alcohol was greater when the initial respiratory quotient was high, i.e. when the combustion of carbohydrate was predominant, than when low, at which time a greater proportion of fat was being oxidized.

[1] Magnus-Levy, *Arch. f. d. ges. Physiol.*, 1894, **55**, 1.
[2] Rosemann, loc. cit.
[3] Higgins, loc. cit.

In the type of experiment described in this work, where the alcohol in the blood is directly calculated, it is obviously possible to test the accuracy of the above deductions. Fig. XV represents the disappearance of alcohol from the blood in a dog, which received 50 c.c. of alcohol in a 20 per cent. solution after it had eaten A. meat, B. fat, C. bread and milk. It is certain that the initial respiratory quotients must have been very dissimilar as the result of eating these different types of food-stuff. With fat the quotient would be low, with bread and milk higher and more approximate to the figure for carbohydrate. It will be seen that the rate of disappearance of alcohol from the blood, and, probably therefore, its rate of oxidation in the body, is practically the same under these

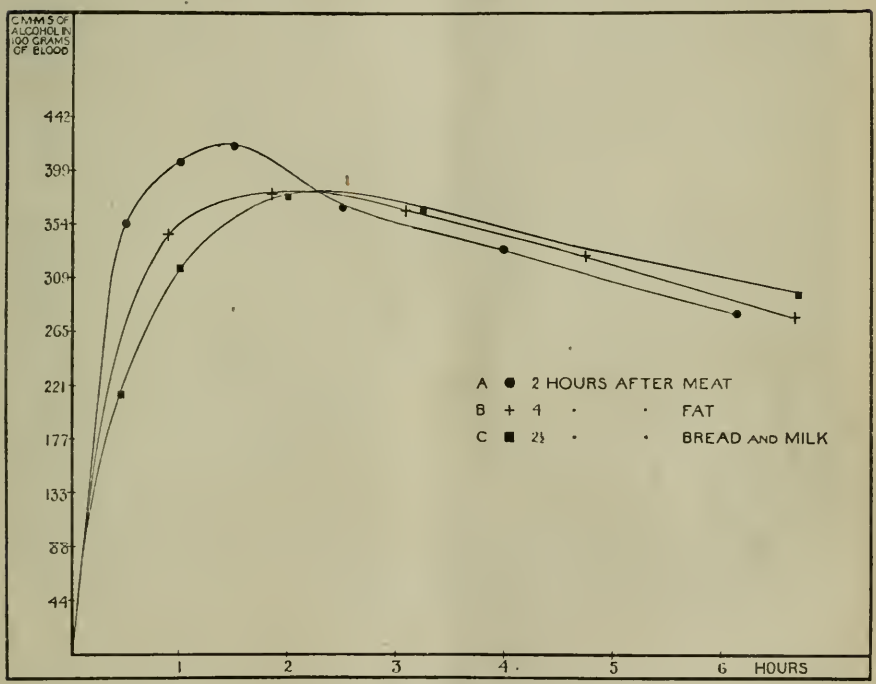

Figure XV.

various conditions. There is no evidence that the rate of combustion of alcohol, when carbohydrate is playing a predominant part, is any higher than when fat is of greater importance. If this is true, then it can no longer be held that the combustion of carbohydrate and fat proceeds at the same relative rate before and after alcohol. An alternative supposition that, when the respiratory quotient is high, more carbohydrate is replaced by alcohol, and when low, a relatively smaller quantity, is more likely to be true in face of the above facts. To what extent the deductions made on the basis of Rosemann's formula are incorrect I do not know. Working under constant conditions without much variation in diet and alcohol consumption, the error may not be of much importance. The point seemed to be of sufficient interest

to merit discussion here. The other basis of Rosemann's formula, viz. that alcohol does not increase the total oxygen consumption, is based on definite experimental evidence adequately confirmed in the experiments of Higgins. It is a point of some importance and shows that, having no specific dynamic action, alcohol must be considered from still another point of view as on a different basis from other food-stuffs. For whatever may be the real explanation of the specific dynamic action of food-stuffs, the stimulating action of proteins, fats, and carbohydrates on the general metabolism is undoubted. Alcohol as a food-stuff, on the other hand, simply replaces certain quantities of carbohydrate and fat, and has no stimulating effect on the metabolic processes of the body and, indeed, does not add to the brightness of the flame. In contrast to the fact that alcohol, in its food effect, does not increase the total heat produced in the body, it is certain that it does increase the heat loss by causing vaso-dilatation of the skin vessels. The result must therefore be a fall in body temperature, which may not be large or important if the animal is receiving a sufficiency of proteins, fats, and carbohydrates as food, but may be serious when, owing to the lack of food, the level of combustion is low. In starvation, for instance, and even more so in starvation combined with exposure, the taking of alcohol, quite apart from its deleterious actions on the central nervous system and neuromuscular mechanism generally, the effect of which is to make the person drowsy and lethargic and thereby to diminish the heat production, may have serious results in consequence of this antipyretic effect. In such cases alcohol does not increase the amount of energy available for immediate use, while it increases the heat loss by causing vaso-dilatation of the skin vessels, an action which is the basis of the improved feeling of warmth and well-being following its use. Were it the case that death due to starvation and exposure resulted from a lack of protein, fat, and carbohydrate stores in the body, alcohol might be more useful in such conditions. Since this is not the case, the benefits that it produces are probably more than balanced by its baneful effects.

Summary.

While it is undoubted that alcohol can supply a large part of the total energy lost by the body (30 per cent. to 40 per cent.), it appears to be different from the other non-nitrogenous food-stuffs in several ways:

(1) Its rate of combustion is independent of the amount circulating in the blood within fairly wide limits.

(2) It has no specific dynamic action, but simply replaces other food-stuffs without stimulating the total combustion processes.

(3) Its rate of combustion is apparently independent of the types of other food-stuffs being metabolized.

XII. The Effect of Exercise on the Rate of Combustion of Alcohol.

The conclusions to be drawn from the experimental results of this work as regards the rate of combustion of alcohol in the body, are in so close agreement with the results obtained by other workers using the methods of calorimetry and respiratory quotients, that it is justifiable to assume that the rate of disappearance of alcohol from the blood is a direct measure of its rate of combustion. The advantage of this method is that the rate of combustion of the alcohol can be determined directly at any moment. With calorimetry and respiratory quotient experiments the interpretation of the results is often indirect, and dependent on hypotheses which in some cases are probably not sound. It may therefore happen that, in these indirect methods of experimentation on alcohol metabolism, points may be missed which are revealed by the direct determination method. The ideal conditions of experimentation would be to supplement the calorimetry methods with estimations of alcohol in the blood, and thereby obtain some direct indication of alcoholic changes at particular moments.

The work of Atwater and Benedict[1] has made it apparent that alcohol can replace fats and carbohydrates isodynamically either in the active or resting states. It is true that they introduce the pharmaco-dynamic or drug-action of alcohol in addition to its nutritive action, in the endeavour to harmonize the results obtained by themselves and other workers of experiments, which were undertaken to demonstrate the sparing effect of alcohol on protein metabolism. This point is not emphasized in the portion of their researches dealing with muscular work. It is probable that this pharmaco-dynamic action was of no consequence in their work experiments because of the small quantities of alcohol used (72 c.c. per diem). After reading Atwater and Benedict's work, the impression is formed that alcohol can be considered on the same basis as carbohydrates and fats as a source of energy in every sense of the word, and the point is of such importance that I think it necessary to lay stress on the following results obtained in experiments showing the effect of exercise on the rate of combustion of alcohol. If Atwater and Benedict's conclusions are true, during mechanical work the rate of combustion of alcohol must increase in the same ratio as the total increase in metabolism. That is to say, alcohol must provide the same percentage of energy during muscular work as at rest. In these experiments, therefore, it would be expected that the rate of disappearance of alcohol from the blood would be greatly increased during exercise.

In the resting experiments the animals were confined for the period of the experiment (about 6 hours) to a small cage, and in the exercise experiments the same animals ran about in the open, and were generally encouraged to do this as vigorously as they were able during the period. In some cases, and more particularly when larger quantities of alcohol were given, the dogs ran behind a bicycle, care being taken not to run them to exhaustion, which is brought on easily in animals under the influence of alcohol. With

[1] Atwater and Benedict, loc. cit.

smaller quantities of alcohol the natural vigour of the dogs was but little affected, and it was unnecessary to use much artificial stimulus to promote activity.

The earlier experiments performed indicated that alcohol was slowly consumed in a dog either active or resting, and that there was but little difference in the rates of oxidation in the two conditions. This point is seen in Fig. XVI, Curves A and B, where

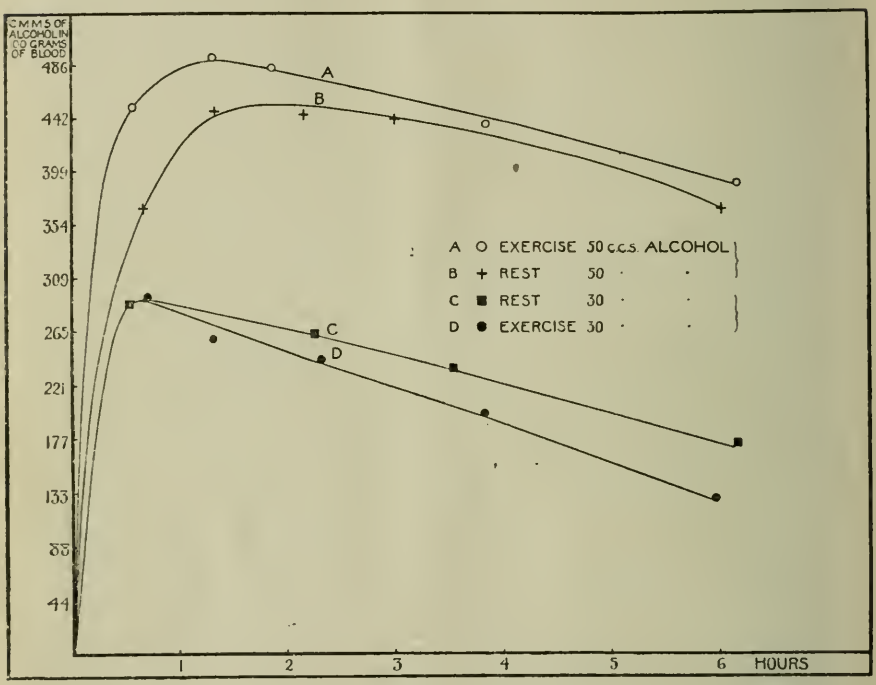

FIGURE XVI.

the rates of disappearance in the two conditions are practically identical. In these experiments the dog received 4·1 c.c. of alcohol per kilogram weight. This and similar results obtained with other dogs spoke against the deductions from Atwater and Benedict's experiments, for, if exercise does not increase the rate of combustion of alcohol, then the substance cannot be considered on an isodynamic basis with carbohydrate and fat, the combustion of both of which is increased by an augmentation of physiological activity. It was, however, thought desirable to diminish the amount of alcohol given. This was done, and Curves C and D were obtained when the dog was given 30 c.c. of alcohol or 2·5 c.c. per kilogram weight. In these curves it will be seen that exercise has increased the rate of disappearance of alcohol from the blood, and, in fact, at the end of 6 hours there is approximately 4 c.c. less alcohol in the body of the dog after exercise, assuming that the concentration of alcohol in the blood is a measure of total alcohol in the body.

This result is even more pronounced in Fig. XVII, where 20 c.c. of alcohol were given in a 20 per cent. solution, or 2·0 c.c. per kilogram weight, to another dog. The exercise Curve C descends more rapidly than the rest Curve A, and roughly speaking the dog in the resting state at the end of 6 hours has about 6 c.c. more alcohol left in its body than after taking exercise. Curve B represents another resting experiment under the same condition as A. In the experiment of Curve D, the animal ran about except for a rest of 1 hour after the alcohol had been injected $1\frac{1}{2}$ hours. Towards the end of the experiment also there was another rest interval. Both of these periods of rest are indicated in the resulting curve by the diminished rate of disappearance of alcohol from the blood. The results obtained with the lower concentration of

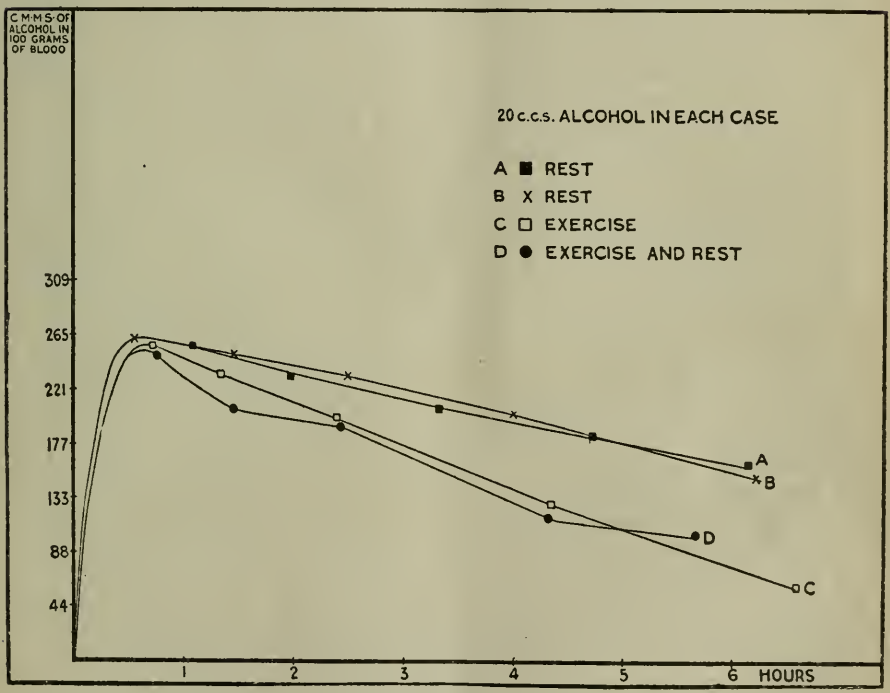

Figure XVII.

alcohol are those where the conditions more closely approximate to the conditions of Atwater and Benedict, who worked with quantities of alcohol which could have only produced low concentration in the blood. In these curves there is distinct evidence that the rate of combustion of alcohol is increased with an increase of bodily activity. With the curves of higher concentration there is no evidence that the rate of combustion of alcohol is altered in any degree by muscular work. Why is there this difference? It may be, of course, that with the smaller concentrations of alcohol in the blood, the dogs were capable of doing much more work than when under greater toxic influence of the drug. The dogs were certainly

much more active. At the same time it must be pointed out that even with the larger doses of alcohol, although easily fatigued, the dogs did a considerable amount of running about, and probably covered 8 to 10 miles in the experimental period. It may well be, however, that the increased activity with the lower concentration accentuated the difference in the rate of oxidation, although it is difficult to understand why there should be no increase with muscular activity at the higher concentrations.

One other factor must be taken into consideration, although on its importance I am not inclined to place much value. The results of Atwater and Benedict show that of the alcohol imbibed only a very small proportion (about 2 per cent.) escaped oxidation, and was excreted unchanged either in the breath or urine. Against these results must be mentioned the work of Völtz and Baudrexel,[1] on dogs specifically designed to determine how much alcohol escaped oxidation under varying conditions. This latter work is not in harmony with that of Atwater and Benedict, for they came to the conclusion that as much as 10 to 12 per cent. of the alcohol drunk could be excreted unchanged in the expired air and urine, and one of the conditions which increased the excreted alcohol most effectively was exercise. The total respiratory ventilation was, under such conditions, largely increased. It is possible, therefore, that some part of the augmented rate of disappearance of alcohol from the blood during the exercise experiments may be due to the greater respiratory exchange and the excretion of alcohol through the lungs. It is further possible that the results of Völtz and Baudrexel may partially explain the inharmonious nature of the curves obtained when greater and less quantities of alcohol were given. With the smaller concentrations the dogs not only ran about more vigorously but also panted to a greater degree, and therefore increased the opportunity for the respiratory excretion of alcohol. Völtz and Baudrexel also showed that larger percentages of alcohol were excreted when more alcohol was given, and therefore it would be expected that the lung excretion factor, if of any importance, would at least be obvious in the exercise experiments of higher alcoholic concentrations (Fig. XVI, Curves A and B). With greater concentration of alcohol in the blood, the diffusion across the lung capillary-walls and lung endothelium ought to be more prominent. However, it is just in these experiments (involving higher concentrations of alcohol in the blood) that there is no difference in the angle of descent of the resting and exercise curves, and no indication of increased alcohol excretion is perceptible. Even if their results are accepted, they could not explain the difference of the amount of alcohol in the blood seen in Fig. XVII curves. Here, at the end of the experiments, there was approximately 6 to 7 c.c. more alcohol in the resting than in the active body. Six c.c. out of a total of 20 c.c. alcohol imbibed is more than could be accounted for by Völtz and Baudrexel's results, where the percentage of alcohol excreted in the breath and urine in no case exceeds 12 per cent. of the total. I conclude, therefore, that alcohol combustion is increased with exercise when the alcohol concentration in the

[1] Völtz u. Baudrexel, *Arch. f. d. ges. Physiol.*, 1911, **142**, 47.

blood is low. When, however, the concentration is increased, the energy obtained from this source in unit time is limited to that of the resting condition, probably in consequence of the toxic action of the alcohol on the cells of the body. The larger doses of alcohol not only diminish the total mechanical work capable of being performed, but also prevent the body from obtaining any increase of energy required for this work from the combustion of the narcotic substance.

In keeping with this suggestion is the rapid fatigue which develops in the more intoxicated dogs, this fatigue being quite apart from the evident sleepiness and laziness associated with alcohol. Since fatigue is largely dependent upon the production of substances such, for instance, as lactic acid, whose presence is notoriously indicative of deficient oxidation, it suggests that a high concentration of alcohol in the body not only limits its own oxidation but also limits the oxidation of other sources of energy, and so brings about the subsequent accumulation of intermediate oxidation products and rapid fatigue.

In the experiments of Fig. XVII, where the dog received 2 c.c. alcohol per kilogram, the energy supplied in the combustion of the alcohol in the resting period is 0·74 calories per kilogram weight per hour. In the exercise experiment with the same dog the energy supplied in this way increased to 1·27 calories per kilogram weight per hour. Unfortunately no figures of the total energy lost in the resting and exercise experiments are available, so that it is impossible to say whether the increase due to exercise is proportional to the increased heat-loss. If the increase in alcohol oxidation is proportional to the total increased energy changes, then it is clear that, in the lower concentrations of alcohol used, the alcohol is being burnt up during exercise isodynamically with the other combustible food-stuffs.

In this connexion, experimental work by Durig[1] on the rate of alcohol combustion is of interest. This worker examined the effect of alcohol on the respiratory quotient of men during climbing. Normally, without alcohol, the effect of climbing a mountain was to cause a decline in the respiratory quotient. When, however, alcohol had been taken before the ascent (1 litre of beer containing 35 grammes of alcohol) the respiratory quotient remained constant or increased. The effect of taking alcohol in a resting condition is to produce a descent in the respiratory quotient (R. Q. for alcohol is 0·667), so that, in the mechanical effort of climbing, the energy was not obtained at the expense of a proportionate combustion of alcohol, but was supplied to a greater degree by carbohydrate oxidation. It appeared that the rate of combustion of alcohol was increased by mechanical work, but under the conditions of Durig's experiment it did not supply the same proportion of energy to the body in the resting and active states. It is necessary to point out that the amount of alcohol in Durig's experiments was smaller than in Atwater and Benedict's experiments (35 grammes against 72 c.c.), and much smaller proportionally than in my own. The alcohol was taken at breakfast by Durig, but

[1] Durig, *Arch. f. d. ges. Physiol.*, 1906, **113**, 213, 341.

at intervals during the course of the day in Atwater and Benedict's experiments.

Whether alcohol can supply the energy for muscular contraction has never, to my knowledge, been decided. Atwater and Benedict on this particular point write: 'That alcohol contributes its share of energy for muscular work is a natural hypothesis which is very probable but not absolutely proven. The hypothesis that the energy of alcohol is not so used is not called for as an explanation of any fact observed in these experiments.' We see, however, from the above-described experiments (with higher concentrations of alcohol), and from Durig's work, that there is evidence that alcohol does not always contribute its share of energy for muscular work, or, at least, does not contribute the same proportion of energy in the resting and active states. Although these results do not prove that alcohol is not a source of energy for muscular contraction, they certainly seem to me to suggest strongly that this is the case. Alcohol combustion does indeed supply heat to the body, but even if the possibility of its providing some of the energy for the contraction of muscles is accepted, it obviously cannot be considered in the same category as other food-stuffs, even when present in the body as in Durig's experiments in minimal quantities, on which occasions its toxic or pharmacodynamic action must have been negligible.

Summary.

The results of these experiments indicate that, whereas alcohol, when present in low concentrations in the body, undergoes combustion at a more rapid rate during exercise than at rest, and therefore supplies a greater amount of energy to the active organism, at higher concentrations it is only oxidized at the same rate in the resting and active animal. In other words, the greater the toxic action of alcohol the more limited is the increase in its rate of combustion by exercise, and the closer do the rates of combustion of alcohol in the active and resting states approximate. Alcohol at high concentrations seems not only to have this self-limiting action on its own oxidative process, but, if fatigue is a true indication of diminished or partial oxidation, to extend its baneful and detrimental influence to the limitation of the oxidation of other combustible material.

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